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CARDIOVASCULAR SYPHILIS

EARLY DIAGNOSIS AND CLINICAL COURSE OF AORTITIS IN THREE HUNDRED AND FORTY-SIX CASES OF SYPHILIS

E. P. MAYNARD JR., M.D.

J. A. CURRAN, M.D.

I. T. ROSEN, M.D.

C. G. WILLIAMSON, M.D.

AND

CLAIRE LINGG, M.A.

BROOKLYN

In the hope of adding to the current knowledge of some of the little understood phases of cardiovascular syphilis, a study was begun in 1927 in the clinics for adults with cardiac disease and syphilis of the Brooklyn Hospital. The plan of the study was as follows: Every patient in the clinic for syphilis who would consent was referred to the clinic for cardiac disease for complete cardiovascular examination. This included taking a history and making a physical examination.[1] Electrocardiograms and teleroentgenograms were taken, and Wassermann tests of the blood were made for nearly every patient. Of more importance, however, is the fact that these patients have been and, it is hoped, will be examined regularly in the clinic for cardiac disease at least every six months. The present paper is a preliminary report, giving an analysis of the facts observed in the first five years of the study.

Some of the major aims of the study are to attempt to describe the course of this disease, to discover in how many patients aortitis develops and what effect treatment has in preventing the development of this complication or in relieving symptoms or prolonging life. In this report we are primarily interested in the early diagnosis of aortitis.

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From the Department of Medicine and the Cardiac Clinic of the Brooklyn Hospital and the Heart Committee of the New York Tuberculosis and Health Association.

Read at a meeting of the Committee on Cardiac Clinics of the New York Tuberculosis and Health Association at the New York Academy of Medicine, Dec. 9, 1932.

1. The standard charts prepared by the research subdivision of the Heart Committee of the New York Tuberculosis and Health Association were used.

The patients come to the clinic for syphilis for treatment on their own motion or are referred by other departments of the hospital. They may be in the primary, secondary or tertiary stages and are referred to the clinic for cardiac disease regardless of whether they have cardiovascular lesions.

In the selection of cases certain definite criteria were established. In the first place, proof of the presence of syphilis beyond reasonable doubt was required. In order to establish a diagnosis of syphilis a history of chancre and one reliable, strongly positive Wassermann reaction were necessary, or, in the absence of a history of primary infection, at least two strongly positive Wassermann reactions. In those cases in which neither a positive history nor a positive Wassermann reaction was obtained, indisputable evidence of syphilis other than of the cardiovascular system, such as tabes dorsalis or dementia paralytica, was regarded as essential.

Next came the much more difficult problem of establishing criteria for the diagnosis of aortitis uncomplicated by aortic insufficiency or aortic aneurysm. We were aware of the existence of a considerable body of competent opinion which holds that, in the absence of aneurysm or gross abnormality of the aorta, it is not safe to make a positive diagnosis of syphilitic aortitis before the appearance of aortic insufficiency.[2] We were familiar, furthermore, with the appearance of the aorta in roentgenograms and with the fluoroscope in syphilitic aortitis.[3] Since a considerable number of persons were included in the study in whom the syphilitic infection was of short duration and in whom the usual clinical symptoms and physical signs that confirm a diagnosis of aortitis would probably be absent, we found it necessary to establish criteria which would enable us to state whether the aorta was enlarged. Except in a few early cases, at least one roentgenogram [4] of the heart and aorta of every patient was taken at a distance of 2 meters, in the usual postero-anterior position and also in the left anterior-oblique view. This examination was supplemented by a fluoroscopic one in many instances. The width of the aortic shadow was measured in the postero-anterior view by the method of Vaquez and Bordet,[5] that is to say, by adding the measurement of the farthest point on the ascending aorta to the right of the midsternal line to the measurement of the farthest point of the aortic knob to the left of the midsternal line. The sum

2. Conner, L. A., in discussion on Steel.[3]

3. Steel, D.: The Roentgenological Diagnosis of Syphilitic Aortitis; Review of Forty Proved Cases, Am. Heart J. **6**:59, 1930.

4. Dr. Ruth Ingraham, roentgenologist of the Brooklyn Hospital, made and interpreted the roentgen measurements.

5. Vaquez, H., and Bordet, E.: The Heart and the Aorta, New Haven, Conn., Yale University Press, 1920.

gives a figure which represents the total width of the shadow comprising the aortic arch and does not include the shadow of the descending aorta. For brevity, this measurement will be referred to as the "width of the aorta" although it is realized that it is in no way descriptive of the true diameter of the aorta. It is not possible to ascertain the latter measurement, especially in young subjects.

To find limits for the width of the normal aortic silhouette proved to be a difficult task, because it is probable that the total transverse diameter varies considerably. Reliance was placed, therefore, on the description of the contour of the ascending aorta and arch, special attention being given to bulging of the ascending aorta as seen in the teleroentgenograms or with the fluoroscope. Bainton's [6] work on the normal aortic silhouette was useful. He found in normal male and female subjects from the second through the sixth decade that up to the age of 50 the extreme variation of the normal aortic silhouette was between 4 and 6.7 cm. for males and between 3.8 and 6.2 cm. for females. Through the age of 59 the highest normal figure was 7 cm. In the present study all aortic measurements of less than 6 cm. were considered normal. In all instances in which the aorta measured between 6 and 7 cm. the films were restudied, or if they were not available the written descriptions and fluoroscopic reports were reviewed. All instances in which the widening of the aortic shadow might be due to a high level of the diaphragm, improper centering of the patient or scoliosis were excluded. The others were carefully studied especially for the presence or absence of bulging of the ascending aorta. When bulging was found those aortas measuring between 6 and 7 cm. were considered abnormal. All aortas measuring 7 cm. or more were classified as dilated.

In order to make a diagnosis of syphilitic aortitis in the absence of aortic insufficiency or aneurysm it is necessary not only to demonstrate bulging or enlargement of the aorta but to recognize other clinical conditions in which the aorta is dilated; these are arterial hypertension, arteriosclerosis and aortic regurgitation of rheumatic origin. Cases of arterial hypertension have been excluded by limiting the group of patients with simple aortitis to those with a systolic blood pressure of less than 140 mm. of mercury. There was only one exception to this rule in the case of a patient whose systolic pressure ranged between 140 and 150. Cases of arteriosclerosis were excluded by limiting the group to patients under 50 years of age. Patients presenting evidence of peripheral arteriosclerosis were placed in a group subsequently referred to as that with aortitis or arteriosclerosis. In order to exclude the

6. Bainton, J. H.: The Silhouette of the Heart and the Aortic Arch, Am. Heart J. **6**:616, 1933.

effect of acute rheumatic infection or dilatation of the aorta, no patient with a history of the diseases included in the rheumatic state was admitted. Pappenheimer and Von Glahn [7] have described lesions of rheumatic fever in the aorta in 2 patients and called the condition rheumatic aortitis. It is not known whether the aorta is dilated in this disease, but it is certain that aortic regurgitation of rheumatic origin causes considerable pulsation of the aorta, which is visible with the fluoroscope. Such cases have been excluded.

To recapitulate, all our patients with simple aortitis are known to have been syphilitic. None has been subject to rheumatic fever or arterial hypertension. None is over 49 years old or presents any evidence of peripheral arteriosclerosis. When the aorta is dilated it is highly probable, therefore, that syphilis is the cause of the dilatation and that a clinical diagnosis of syphilitic aortitis is justified.

One of the aims of this study, as has been mentioned, is to try to discover a method by which the diagnosis of syphilitic aortitis can be made much earlier than in the past. By the time the aortic second sound has become hollow and accentuated, a systolic murmur has appeared at the aortic area or symptoms such as paroxysmal dyspnea or substernal pain have developed, the syphilitic process in the aorta is well advanced. We have turned to the x-ray film and fluoroscopy to discover whether these methods can throw further light on the possibility of early detection.

MATERIAL

Incidence.—Three hundred and forty-six patients who satisfied the criteria just described were studied. Syphilis was of the acquired type except in 14 patients (4 per cent), in whom it was congenital. Less than half (41.9 per cent) presented evidence of cardiovascular syphilis. This is a higher incidence than has been reported by other observers. Turner [8] found an incidence of 10.1 per cent in 6,420 patients in the late stages of syphilis. What the percentage of patients infected with syphilis who show involvement of the cardiovascular system ultimately might be may be learned from a study of autopsies. Langer [9] maintained that from 70 to 80 per cent of all syphilitic patients among 23,105 who came to necropsy at the Rudolf Virchow Krankenhaus presented evidence of involvement of the aorta. Moore, Danglade and

7. Pappenheimer, A. M., and Von Glahn, W. C.: A Case of Rheumatic Aortitis with Early Lesions in the Media, Am. J. Path. **2**:15, 1926; Studies in the Pathology of Rheumatic Fever, ibid. **3**:583, 1927.

8. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, Bull. Johns Hopkins Hosp. **46**:159, 1930.

9. Langer, E.: Die Häufigkeit der luetischen Organveränderungen insbesondere der Aortitis luetica, München. med. Wchnschr. **73**:1782, 1926.

Reisinger [10] placed the figure based on evidence collected in this country and abroad at between 80 and 90 per cent.

Sex.—The preponderance of males with syphilis, as compared with females (a proportion of approximately 2:1), is in agreement with other observations (table 1). Lamb and Turner [11] found it to be 3:1.

Race.—Since this study was made in a northern community where the number of Negroes is small, the white race was found to make up a large percentage of the cases (white race, 81 per cent, and colored race, 19 per cent). The incidence of cardiovascular syphilis was only slightly higher among the colored race (45.5 per cent), as compared with 41.8 per cent among the white patients. Turner [8] found a somewhat higher ratio of colored patients to white patients in a southern population—11.4:7.2 per cent. About one third of the white patients were females, while approximately one half (48.5 per cent) of the Negro patients were females.

TABLE 1.—*Incidence of Syphilis According to Sex*

	Both Sexes		Males		Females	
	Number	Percentage	Number	Percentage	Number	Percentage
Evidence of cardiovascular syphilis...	145	100	101	69	44	31
No evidence of cardiovascular syphilis	201	100	119	59	82	41
Total number of cases.....	346	100	220	64	126	36

Age at Occurrence of Primary Lesion.—Syphilis is usually acquired in late adolescence and early adult life. In 190 patients (55 per cent) the date of the occurrence of the primary lesion was known. One fourth of our patients acquired syphilis before the age of 21; one-half before the age of 25, and three-fourths before the age of 30 (fig. 1).

Interval from Occurrence of Primary Lesion to First Observation in Clinic for Cardiac Diseases.—In order to describe the natural history of cardiovascular syphilis it is necessary to know the age at which infection occurred. Half of our patients were examined within ten years of the time after the primary lesion was acquired, but the average period for the whole group was thirteen years. It is noteworthy that 25 per cent were examined within one year after the occurrence of the initial lesion, owing to the fact that the clinic for syphilis referred cases promptly (fig. 2).

10. Moore, J. E.; Danglade, J. H., and Reisinger, J. D.: Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm, Arch. Int. Med. **49**:766 (May) 1932.

11. Lamb, A. R., and Turner, K. B.: Cardiovascular Syphilis in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1932, vol. 4, chap. 3, p. 337.

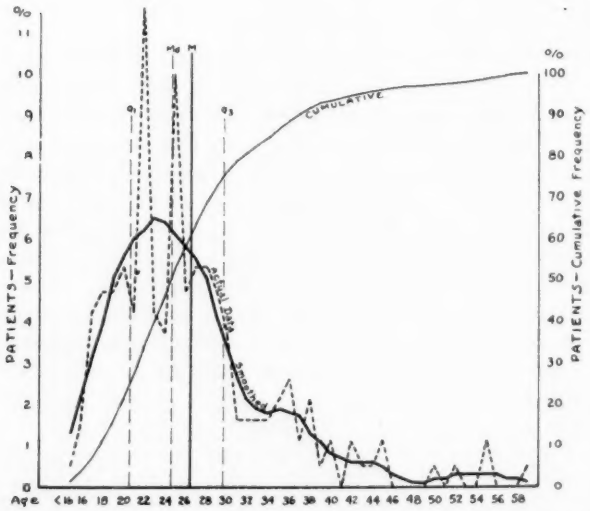


Fig. 1.—Age at the occurrence of the primary lesion. In this figure and in figures 2, 3 and 4, *Q1* indicates the data for one fourth of the patients; *Q3*, for three fourths; *Md*, for one half, and *M*, for the average number.

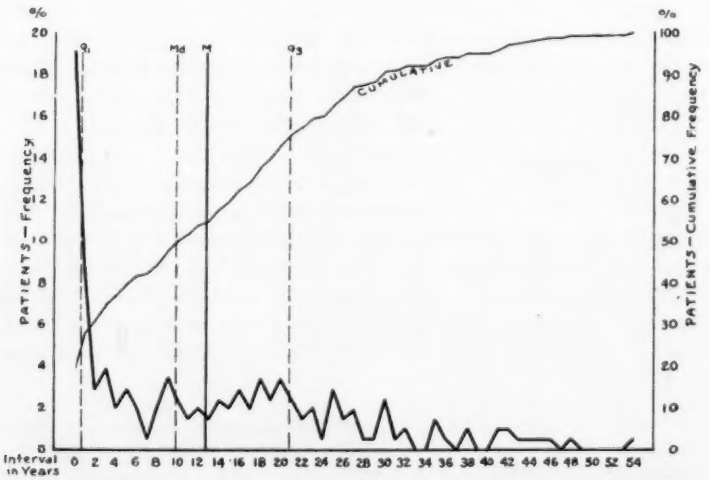


Fig. 2.—Interval from the occurrence of the primary lesion to the beginning of observation in the clinic for cardiac diseases.

Interval from Occurrence of Primary Lesion to Discovery of Cardiovascular Syphilis.—It has frequently been reported that the "latent" period, that is to say, the interval between the occurrence of the initial lesion and the onset of symptoms and physical signs of cardiovascular disease, is long, usually from sixteen to twenty years. DeGraff,[12] in an analysis of the records of about 200 deceased patients who had been treated for cardiovascular syphilis in Bellevue Hospital, found that the average interval from infection to the discovery of heart disease was twenty-two and seven-tenths years. He found, further, that more than two thirds had applied for treatment in the clinic for cardiac disease within two years after the symptoms were first experienced and that

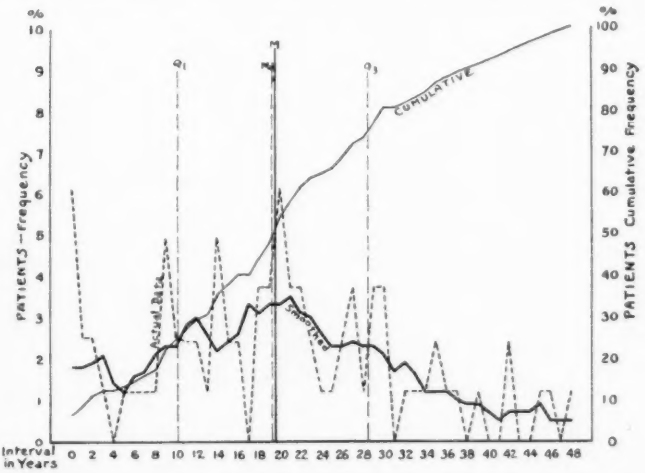


Fig. 3.—Interval between the occurrence of the primary lesion and the discovery of cardiovascular syphilis.

a diagnosis of heart disease was made simultaneously with the first complaint in more than half. In only 10 per cent was the interval from infection to the discovery of heart disease less than ten years.

In our group, which, as has been pointed out, came under observation in the clinic for cardiac disease earlier after the initial infection than is customarily the case, one fourth showed evidence of cardiovascular syphilis within ten years after the occurrence of a chancre (fig. 3), although the mean interval was twenty years. Discovery of cardiovascular involvement must not be taken to indicate the time at which the heart becomes infected. At present involvement can be recognized only after gross changes have taken place in the aorta.

12. Personal communication to the authors.

Interval from Occurrence of Primary Lesion to Onset of Cardiac Symptoms.—The next milestone in the course of cardiovascular syphilis is the point at which the damage has become great enough to cause symptoms. Under cardiac symptoms are included palpitation, precordial pain and dyspnea. These symptoms, in the form of sudden onset of circulatory embarrassment and paroxysmal dyspnea, are not believed to be characteristic of aortitis. Since we were trying to discover means for the earliest possible recognition of cardiovascular syphilis, it seemed desirable to include any symptoms that might direct attention to the heart. Almost half of the patients (49 per cent) who presented cardiovascular syphilis complained of symptoms. These began, on the average, twenty years after infection (fig. 4).

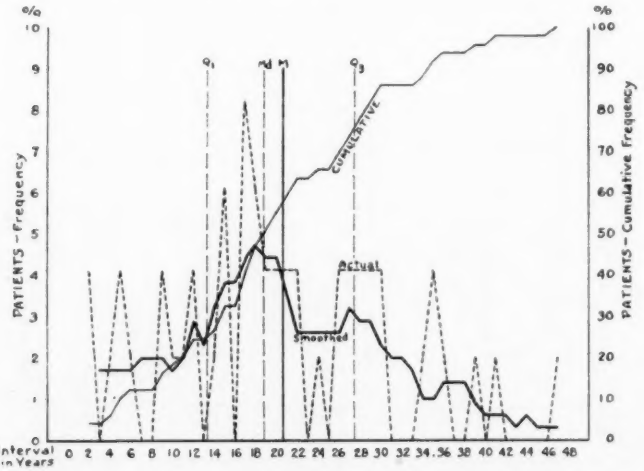


Fig. 4.—Interval between the occurrence of the primary lesion and the onset of cardiac symptoms.

The mean interval from the occurrence of the primary lesion to the discovery of heart disease and that from the occurrence of the lesion to the onset of symptoms therefore coincide. In our experience symptoms were conspicuous by their absence in the early cases and were not helpful in the early diagnosis of aortitis. Of 59 patients with uncomplicated aortitis, 13 (22 per cent) presented symptoms referable to the heart. In these patients aortic insufficiency, aneurysm or disease of the coronary arteries had not developed.

Etiologic and Anatomic Diagnosis.—In any study of the course of cardiovascular syphilis it is important to separate patients suffering from syphilis alone from those suffering also from arteriosclerosis, for example.

In 93 patients syphilis alone was the etiologic factor. Patients over 50 years of age, as well as those who had a history of rheumatic disease or clinical evidence of arteriosclerosis or arterial hypertension, were, as has been stated, excluded. There were, in addition, 7 cases of cardiovascular syphilis complicated by heart disease clearly due to arterial hypertension or to rheumatic fever. In another, larger group of patients either 50 years old or suffering from peripheral arteriosclerosis, it was impossible to be certain whether widening of the aorta was due to syphilis or arteriosclerosis. These cases, which numbered 45, were designated as cases of syphilis or arteriosclerosis (table 2). The high percentage of cases of uncomplicated aortitis (40.6) in which syphilis alone was the etiologic factor is striking. Fifteen per cent of the

TABLE 2.—*Anatomic Diagnosis*

Anatomic Diagnosis	Etiology					Percentage of Total
	Syphilis	Syphilis and Hypertension	Rheumatic Fever	Syphilis or Arteriosclerosis	Total	
Total number	93	5	2	45	145	100
Aortitis	59	..	..	..	59	40.6
Aortic insufficiency	1	..	..	..	1	0.7
Aortitis and aortic insufficiency	14	..	..	..	14	9.6
Aneurysm	12	..	..	..	12	8.3
Aneurysm and aortic insufficiency	5	..	..	..	5	3.5
Aortitis, aortic insufficiency and coronary disease	2	..	..	..	2	1.4
Aortitis and enlarged heart	..	5	..	..	5	3.5
Aortitis and rheumatic heart disease	..	..	2	..	2	1.4
Aortitis or arteriosclerosis of aorta	..	..	..	39	39	26.9
Aortitis or arteriosclerosis and fibrosis of myocardium	..	..	..	6	6	4.1

patients showed evidence of aortic insufficiency, and 11.8 per cent had aortic aneurysm. In only 2 cases was a diagnosis of narrowing of the coronary arteries due to syphilis made. This diagnosis was confirmed at autopsy in both instances.

Enlargement of the heart, often of marked degree, occurs, as is well known, when aortic incompetency has developed. The question whether the heart enlarges during the stage of aortitis and before the development of aortic insufficiency has not been answered clearly. Patients with uncomplicated syphilitic aortitis showed some degree of enlargement of the heart (19, or 32.2 per cent). When aortic insufficiency made its appearance the percentage rose (78.5). Patients with aneurysm without aortic insufficiency showed enlargement (41.7 per cent), especially when aortic insufficiency was also present (80 per cent; table 3). Enlargement of the heart was present, in short, in about one third of the patients with uncomplicated aortitis and in almost four fifths when aortic insufficiency had developed.

Incidence of Cardiovascular Syphilis Relative to the Date of Infection.—Since we were particularly interested in discovering methods of recognizing cardiovascular syphilis early we classified our cases into five groups [13] according to the duration of the syphilitic infection, depending on whether evidence of cardiovascular disease appeared within three, from four to nine, ten to nineteen, twenty to twenty-nine or thirty or more years after the appearance of a chancre. The following data were obtained:

Group 1: In the first group, 8 cases (14 per cent) satisfied our criteria for the diagnosis of cardiovascular syphilis; all the patients showed aortitis and nothing else. Three other patients presented signs

Table 3.—*Enlargement of the Heart*

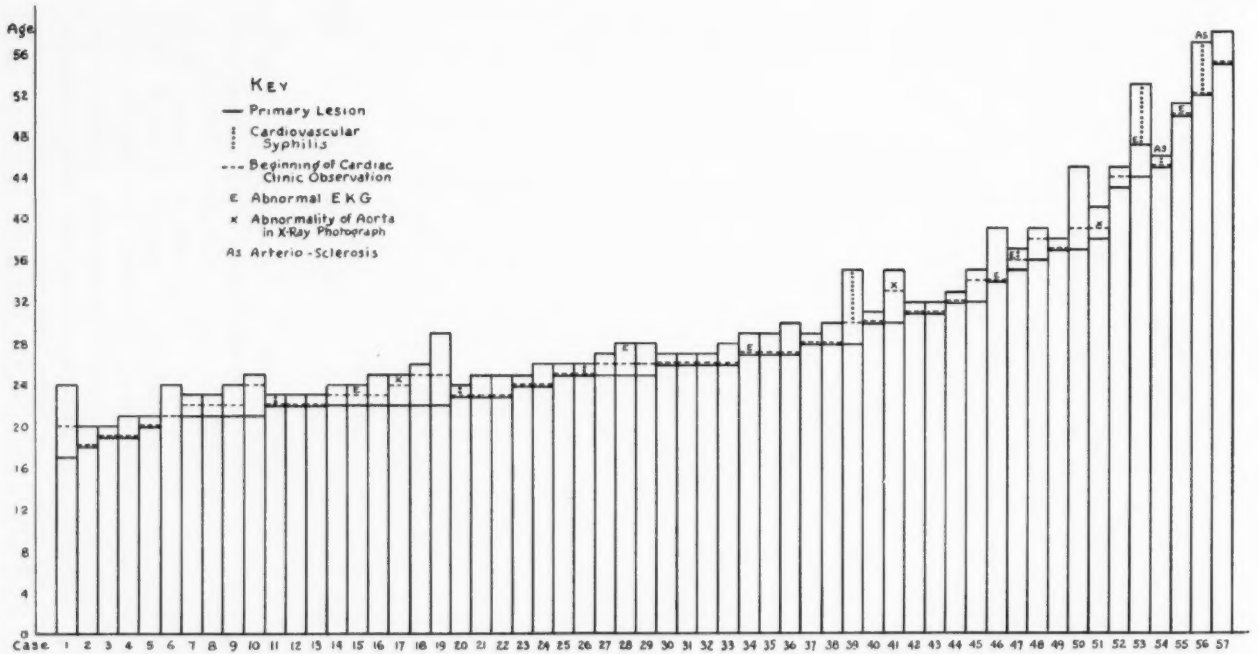
Etiology	Anatomic Diagnosis	Total Number of Cases	Enlargement of Heart	
			Number	Percentage
Syphilis	Aortitis	59	19	32.2
	Aortic insufficiency	1	0	0
	Aortitis and aortic insufficiency	14	11	78.5
	Aortitis, aortic insufficiency and coronary disease	2	1	50.0
	Aneurysm	12	5	41.7
	Aneurysm and aortic insufficiency	5	4	80.0
	Total	93	40	43.0
Syphilis and hypertension	Aortitis and enlargement of heart	5	5	100.0
Syphilis and rheumatic fever	Aortitis and rheumatic valvular disease	2	1	50.0
Syphilis or arteriosclerosis	Aortitis or arteriosclerosis	45*	23	51.0
Total		145	69	47.6

* Fibrosis of the myocardium was present in six cases.

of abnormality of the aorta in roentgenograms, and 5 others showed electrocardiographic abnormalities. The significance of these is discussed later. Forty-one (72 per cent) were entirely free from any signs of cardiovascular change. It should be stressed that only one of the entire group complained of symptoms referable to the heart (fig. 5).

Group 2: Of patients not seen in the clinic for cardiac disease until from four to nine years after primary infection, 6 (28.6 per cent) revealed the presence of aortitis; 2 of these presented also aortic insufficiency and 1 an aneurysm. Eleven were entirely free from any abnormality referable to the heart (52 per cent, as compared with 72 per cent in group 1). In case 2 the history of the symptoms was unreliable (fig. 6).

13. We included in these groups only those patients concerning whom the life history of the disease, from the occurrence of the chancre to the findings at the last examination, was known.


Age
56
52
48
44
40
36
32
28
24
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16
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0
Case 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57
KEY
— Primary Lesion
Cardiovascular Syphilis
--- Beginning of Cardiac Clinic Observation
E Abnormal E K G
× Abnormality of Aorta in X-Ray Photograph
As Arterio-Sclerosis

Fig. 5. (group 1).—Data for patients at the beginning of observation in the clinic for cardiac diseases less than five years after the occurrence of the primary lesion. In this and the following figures, *E K G* means electrocardiogram.

Lamb and Turner [11] found few patients who presented symptoms or signs in the latent period (10 of 148). These died of some cause other than syphilis, though postmortem examination revealed the presence of syphilitic aortitis. Clinical evidence of cardiovascular syphilis developed, however, within less than ten years (in 12.3 per cent of the remaining 138 patients). The findings for this group differ slightly, the number affected within the first nine years being higher (18 per cent of 78 cases).

GROUP 3: Thirty-seven patients were referred to the clinic for cardiac disease from ten to nineteen years after infection. The incidence of cardiovascular syphilis among these is higher (in 21, or 56.8 per

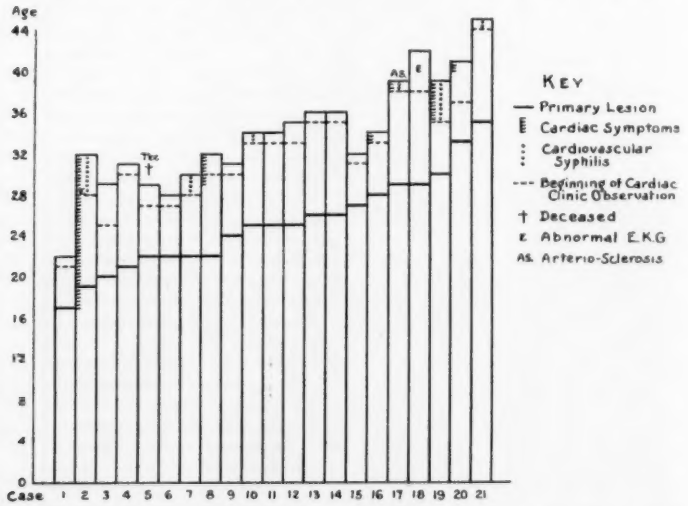

Fig. 6 (group 2).—Data for patients at the beginning of observation in the clinic for cardiac diseases from four to nine years after the occurrence of the primary lesion.

cent). Heart failure developed in 2 patients; 1 of these had two periods of decompensation due to aneurysm or aortic insufficiency and enlarged heart. In certain cases (10) some degree of arteriosclerosis was also present. Usually there were complaints of symptoms referable to the heart (in 9 of the patients with arteriosclerosis and 10 others). The number of those having symptoms rose from 28.6 to 51.3 per cent. Only 9 patients were entirely free from signs of cardiac disease (fig. 7). Arteriosclerosis had, of course, begun to make its appearance in this group and may account for some of the symptoms.

GROUP 4: Syphilitic heart disease was present after a lapse of from twenty to twenty-nine years in three quarters of the cases (77.8 per

cent). Either aneurysm or aortic regurgitation appeared in 40 per cent; among them were 4 cases of heart failure (fig. 8). Arteriosclerosis was now more commonly observed (in 44 per cent), and symptoms frequently made their appearance (in 78 per cent).

GROUP 5: Thirty or more years after infection syphilitic heart disease was present in all but 2 patients (15, or 88.2 per cent). Seven showed either aneurysm or aortic incompetence; and 4, heart failure

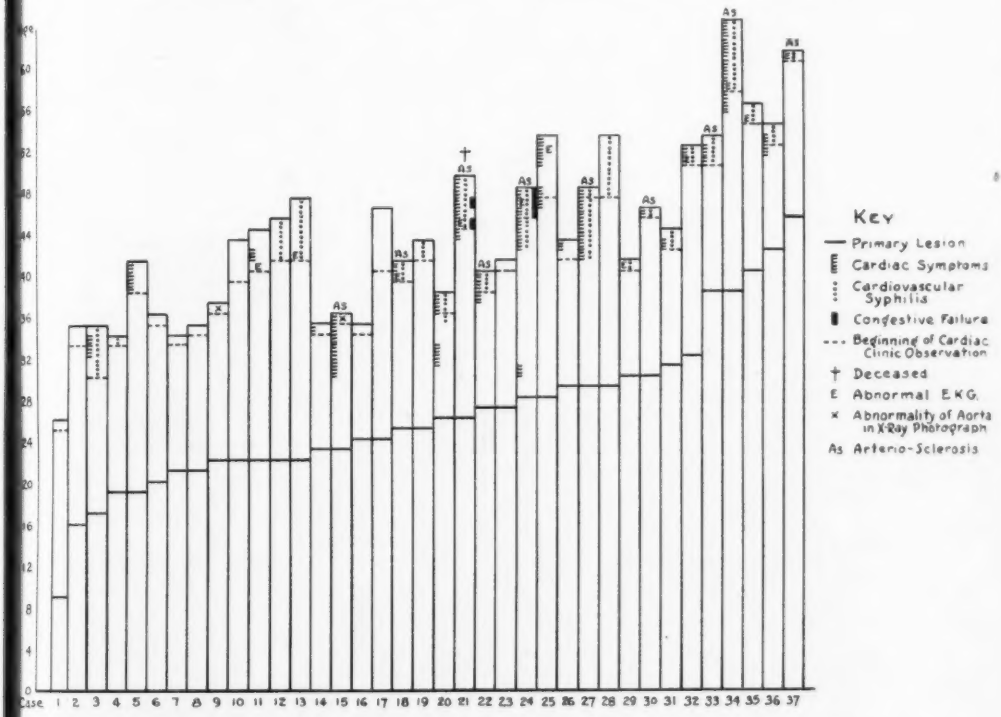
Key
Primary Lesion
Cardiac Symptoms
Cardiovascular Syphilis
Congestive Failure
Beginning of Cardiac Clinic Observation
† Deceased
E Abnormal E.K.G.
× Abnormality of Aorta in X-Ray Photograph
As Arterio-Sclerosis
Case 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37

Fig. 7 (group 3).—Data for patients at the beginning of observation in the clinic for cardiac diseases from ten to nineteen years after the occurrence of the primary lesion.

complicated by aneurysm or aortic insufficiency or both. Arteriosclerosis was frequent (in 12 patients), but in no instance was it the primary cause of heart failure. Most of the patients in this group (76.5 per cent) complained of symptoms referable to the heart.

Comment: Certain patients in the five groups complained of cardiac symptoms before they came under observation. This group was studied in greater detail. It was found that in group 1, no patients, and in

group 2, only 1, complained of symptoms before the diagnosis of aortitis was made. These two groups together included all the patients in whom syphilitic infection was of short duration (less than ten years). Only 1 patient of the 14 complained of symptoms that might have led to the detection of aortic syphilis. As the duration of the infection lengthened and also as the patients grew older, symptoms began to make

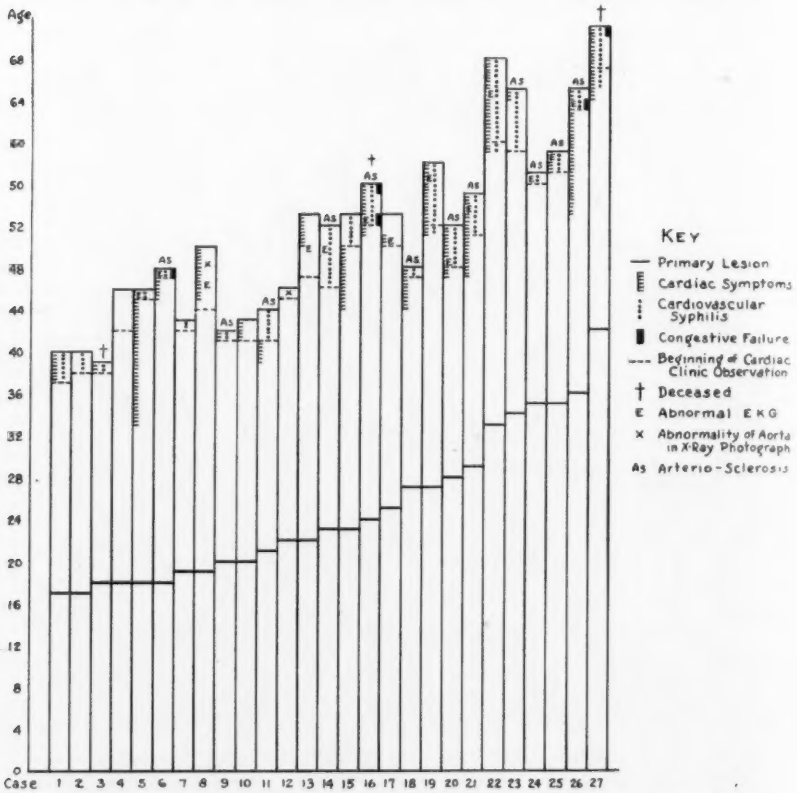

Fig. 8 (group 4).—Data for patients at the beginning of observation in the clinic for cardiac diseases from twenty to twenty-nine years after the occurrence of the primary lesion.

their apearance more often. In the early cases (those of less than ten years' duration) symptoms were not helpful in making a diagnosis.

The study of patients grouped according to the duration of the infection brought out strikingly the steady increase in the development of symptoms and lesions due to cardiovascular syphilis (table 4).

Symptoms tended not to be detected until after the discovery of aortic involvement in the younger groups. Finally, a steady increase was demonstrated in the appearance of cardiac symptoms in the older groups, even when no syphilitic involvement of the aorta had taken place.

Changes in the Electrocardiograms.—An analysis was made of the electrocardiograms for those patients in whom the duration of syphilitic

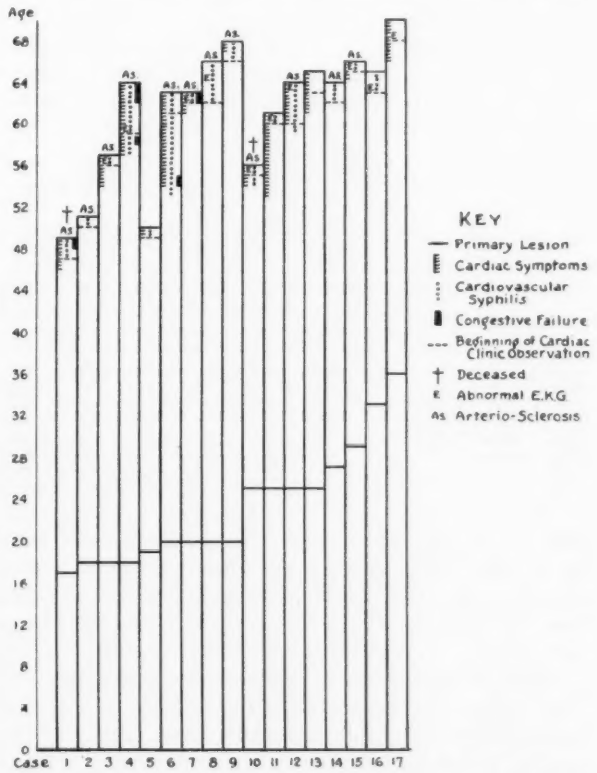

Fig. 9 (group 5).—Data for patients at the beginning of observation in the clinic for cardiac diseases thirty or more years after the occurrence of the primary lesion.

infection was known. All deviations from the normal were recorded and tabulated, but only those changes were studied which might be of clinical significance. These included auricular fibrillation, prolonged auriculoventricular conduction, partial heart block, low voltage and prolonged duration of the QRS complex, slurred and splintered QRS complex in all leads, depression or elevation of the ST segment and

significant negativity of the T wave. We found significant changes rarely in the early cases (in 10.4 per cent) when syphilis was the only etiologic factor. When arteriosclerosis and hypertension were also present the incidence of significant changes doubled (20 per cent).

After a longer duration the incidence of significant changes greatly increased (52 per cent). When other conditions played a rôle the incidence was lower (23.7 per cent), but since there were only 38 such cases the sample is too small to be of value for analysis. Within one year after the appearance of a chancre no changes were found in a former study.[14] Now, in a much larger series including the same patients significant electrocardiographic changes were still rare (in 10.4 per cent) after ten years.

Postmortem Lesions.—Of thirteen patients who died, 4 were examined post mortem. As was anticipated, lesions of syphilitic aortitis

TABLE 4.—*Evidence of Cardiovascular Disease, Cardiac Symptoms and Heart Failure in Cases of Early Versus Late Syphilis*

Group	Years from Occurrence of Primary Lesion to Observation in Clinic	Number of Cases	Mean Age at Occurrence of Primary Lesion	Cardiovascular Syphilis		Cardiac Symptoms		Congestive Heart Failure		No Cardiac Abnormality	
				Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
1	0- 3	57	28	8	14.0	..	....	..	....	41	71.9
2	4- 9	21	25	6	28.6	6	28.6	..	....	11	52.4
3	10-19	37	26	21	56.8	19	51.3	2	5.4	9	24.3
4	20-29	27	25	21	77.8	21	77.8	4	14.8	..	....
5	30	17	23	15	88.2	13	76.5	4	23.5	..	....

were present in all of them. In 3 there was aortic insufficiency; in 1 myocardial fibrosis and in 1 syphilitic disease of a coronary artery were also discovered. The width of the aortic shadows in roentgenograms of these 4 patients measured 6.6, 8, 9.5 and 10.3 cm., respectively. The first figure offers proof that syphilitic aortitis can occur when this measurement is between 6 and 7 cm. Besides aortitis, occlusion of a coronary artery due to syphilis, degeneration of the heart muscle and, in 2 instances, aneurysm of the arch of the aorta were present. There were no instances of syphilis of the myocardium, nor was a clinical diagnosis of syphilitic myocarditis made in the entire series of 346 patients. The changes in the myocardium were degenerative and due either to interference with the coronary circulation at the mouths of these vessels or to the effect of aortic insufficiency.

One case should be reported briefly because it furnishes further proof that syphilitic aortitis can develop to a marked degree within a short time after the appearance of a chancre.

14. Ingraham, R., and Maynard, E. P., Jr.: The Electrocardiogram and Teleroentgenogram in Early Syphilis, Am. Heart J. **6**:82, 1930.

E. S., a Negro, had a chancre in 1927, at the age of 35. The first symptoms referable to the heart were noted in October 1928. Disease of the heart was discovered in December, and he died of congestive heart failure in May 1929, two years after the onset of syphilitic infection. He suffered from anginal pain on exertion. A clinical diagnosis of syphilitic aortitis, aortic insufficiency and syphilitic disease of a coronary artery with myocardial failure was made. Syphilitic aortitis, occlusion of the right coronary artery 6 mm. from its ostium due to syphilis and degeneration of the heart muscle were present.[15] The histologic diagnosis was syphilitic inflammation. There was an organized and canalized thrombus. The myocardium showed areas of recent myocardial softening and other areas of scar formation. The more recent areas were the larger. The vessels in the myocardial fat showed some thickening but no significant or characteristic internal changes. The areas of reaction in the myocardium contained numerous lymphocytes, newly formed fibroblasts and early scar tissue. In this case syphilitic aortitis had developed rapidly about strategic points—the openings of the coronary vessels. The nutritional damage to the myocardium was sufficient to cause death within two years.

Congenital Syphilis.—Fourteen cases of congenital syphilis are included in this study. Seven patients showed no cardiovascular lesion whatever. Of the remaining 7, 2 exhibited evidence of rheumatic heart disease, 1 of congenital malformation of the heart, 1 of cardiac enlargement of unknown etiology and 3, in the fifth decade of life, of arterial hypertension, enlarged heart and widening of the aorta. A diagnosis of syphilitic aortitis was not made because of the presence of arterial hypertension.

The aortic shadows in the teleroentgenograms of these 14 patients measured between 6 and 6.9 cm. One, that of a man 54 years of age, gave aortic measurements of 6.2 cm.; in another patient, 45 years of age, aortic enlargement occurred in association with arterial hypertension, and in a third in association with congenital malformation of the heart. There were 2 patients whose aortas measured more than 7 cm., but arterial hypertension was present in both. In each instance, when the aortic measurement was abnormal there was, therefore, some condition beside syphilis to which dilatation might be attributed.

In this group of patients with congenital syphilis there was none for whom we could safely make a clinical diagnosis of syphilis of the aorta.

Duration of Disease.—Although this study does not concern itself with the prognosis, an attempt has been made to compare the course of events in these cases with that studied by Grant,[16] who for ten years, beginning in 1919 to 1921, collected and analyzed the histories of 189 army pensioners, all of whom suffered from syphilitic aortic

15. Dr. James Denton, pathologist at the Brooklyn Hospital, made the postmortem examination.

16. Grant, R. T.: After Histories for 10 Years of a Thousand Men Suffering from Heart Disease, Heart **16**:311 (June) 1933.

regurgitation. Analysis of his histories shows that, on the average, his patients came under observation twenty-four years after initial infection —eleven years later than the average patient in the present study. This difference is explained by the fact that Grant's series was limited to patients with aortic insufficiency or aneurysm, conditions which are not often diagnosed until late in the course of the disease. When patients with these lesions alone are considered in the present study the interval between infection and first observation was, on the average, three years shorter than that reported by Grant. Symptoms first appeared, on an average, twenty years after the occurrence of the chancre in both groups.

It is not possible to make a comparison of the duration of life in the two series because the number of cases of aortic insufficiency in the present study is too small (15) to give it statistical significance and the number of patients who died is limited to 13. But Willius [17] made a study of 100 patients, having taken care to include only those for whom the date of infection and the date of death (the duration of the disease) were known. The average duration was twenty-four years. In a sample of 200 similar cases, DeGraff [18] found the average duration to be twenty-six years; and the interval from the onset of symptoms to death, 3 years. Cabot [19] regarded these intervals as being even shorter—from fifteen to twenty years, and two years, respectively. Grant concluded that "the prognosis, though poor, is not so gloomy as it is usually thought to be"; he based this opinion partly on the fact that his patients have lived longer than the two or three years after observation usually assigned. He ventured this conclusion because 38 per cent of his patients were still living at the end of his ten year period of observation.

It should be pointed out, however, that the date of diagnosis is not a satisfactory point from which to relate the prognosis, because it varies with the skill of the observer and the time after infection when patients first present themselves. Probably Grant's prognosis, based on the length of life after the first observation, is better than that of others, because by his method of selection through the army his patients came under observation sooner and their illness was diagnosed earlier. The fact remains, however, that Grant did not take into consideration the date of infection of his patients. Our analysis of his published case records reveals twenty-eight years as the average duration of the disease (from infection to death) for the deceased, while those who lived longer than his ten year period of observation have already lived an average of thirty-four years. This living group, however, comprises

17. Willius, F. A.: A Study of the Course of Syphilitic Cardiovascular Disease, Am. Heart J. **6**:113, 1930.

18. Personal communication to the authors.

19. Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926.

only 19 patients.[20] The mean duration from the onset of symptoms to death was seven and six-tenths years, while 66 surviving patients lived an average of thirteen years.

It appears, therefore, that in cases in which the facts are known, the duration (from infection to death) of the disease was twenty-four years (Willius), twenty-six years (DeGraff) and twenty-eight years (Grant) —no great difference (fig. 10). Among Grant's patients who were still living, the duration in 19 cases was, however, thirty-four years. The interval from the onset of symptoms to death was two years (Cabot), three years (DeGraff), and seven and six-tenths years (Grant). Among Grant's patients who were still living the interval was thirteen years. The last group was alive five years after the average duration of the disease in Grant's deceased patients. This seems to point to the impropriety of separating the analysis of cases of living and dead patients.

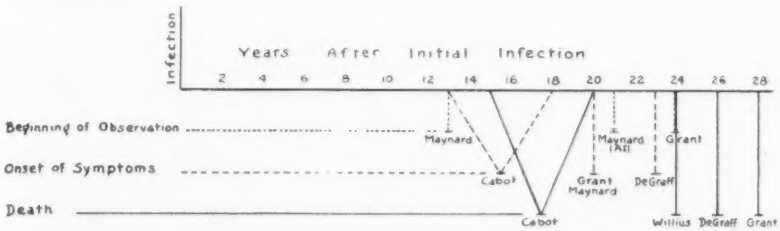

Fig. 10.—Factors pertaining to the duration of cardiovascular syphilis according to various observers. The intervals expressed in this chart (from infection to the beginning of observation, the onset of symptoms and death) represent, in each case, mean averages.

The fact that Grant's sample is made up of ex-service men, which necessarily excludes persons with cardiovascular syphilis who must have been rejected for military service because of advanced disease, as well as those who may have been recruited and yet not have survived the strain of the war, may account for this somewhat better prognosis than is usually reported. Emphasis should be laid on the need for proper selection of cases if comparison is desired on the course of events in groups of cases studied in different clinics. When groups of identical or similar composition are studied the likeness rather than the difference of the experience is striking. It is possible that as our methods of diagnosis improve and as syphilitic patients come to be examined earlier and more carefully, the length of life from the time diagnosis is made to death may increase. A true idea of the prognosis can, however,

20. This group is limited to 19 patients because in the other instances the date of infection could not be ascertained.

be obtained only by relating the duration of the disease to a definite period in its natural history—in this instance, the date of infection—rather than to arbitrary points of reference, such as the time at which physicians establish relations with given patients.

GENERAL COMMENT

The present investigation was planned in order to study the natural history of syphilitic infection in relation to its effect on the cardiovascular system. Patients in the Brooklyn Hospital who were infected with syphilis were examined, with special attention directed to the heart and aorta. By this method it was hoped that syphilitic involvement of the aorta could be detected earlier than is customary. The high incidence of syphilitic aortitis that was found, namely, in 40.6 per cent of all the patients examined, seems to have justified this expectation. It emphasizes, furthermore, the necessity for periodic systematic examination, including the use of roentgenography and fluoroscopy.

Many authors have mentioned the sudden onset of symptoms of circulatory embarrassment as one of the essential points in the diagnosis of syphilitic aortitis. Carter and Baker [21] gave it as the first in their list of seven criteria for the diagnosis of cardiovascular syphilis. Moore, Danglade and Reisinger [10] found that symptoms were more often insidious than abrupt in onset and placed the nature of the onset of symptoms second only to the appearance in roentgenograms in diagnostic importance. Each of these studies was concerned with cases in which the disease was far advanced. In the present study it was found that symptoms referable to the heart were not helpful in making an early diagnosis of syphilitic aortitis. Those patients for whom this diagnosis was established within three years after the date of infection presented no cardiac symptoms whatever. Even when the group is included in which the diagnosis was made within ten years after the appearance of a chancre, symptoms referable to the heart were rarely encountered.

Physical signs, also, such as an accentuated hollow aortic second sound and an aortic systolic murmur, which are usually regarded as characteristic of this disease, were absent and could not be relied on in attempting to make an early diagnosis of syphilis of the aorta. The use of the roentgen method appears, however, to be extraordinarily valuable in deciding on the presence of aortitis in the absence of aortic insufficiency or aneurysm. The measurements usually accepted as descriptive of the normal aortic silhouette were found to be satisfactory, but reliance must, nevertheless, be placed on the skill of a competent

21. Carter, E. P., and Baker, B. M., Jr.: Certain Aspects of Syphilitic Cardiac Disease, Bull. Johns Hopkins Hosp. **48**:315 (May) 1931.

roentgenologist in interpreting the form of the aortic shadows. Abnormal contours, especially of the ascending aorta, are important evidence in deciding on the existence of aortitis.

SUMMARY

Three hundred and forty-six patients with syphilis were studied. One hundred and forty-five (41.9 per cent) showed positive evidence of cardiovascular syphilis.

There were 14 adult patients with congenital syphilis. In none of these was evidence of syphilis of the heart or aorta found.

The date of occurrence of the primary lesion was known in about half of the patients (55 per cent). The average age at which infection occurred was 26 years. In a quarter of the patients studied the chancre appeared before the age of 21.

One fourth came for examination within one year, and one half within ten years, after the occurrence of the initial lesion.

Evidence of cardiovascular syphilis was found within ten years after the appearance of the chancre in one fourth of the cases, although the average interval from infection to the discovery of heart disease was twenty years. Symptoms were somewhat slower in making their appearance. One fourth of the patients complained of symptoms within fourteen years after the development of the primary lesion. The average interval before symptoms occurred was twenty years.

Evidence of cardiovascular syphilis was found within the first three years after the appearance of the chancre in 8 patients (14 per cent). One in the entire group complained of symptoms referable to the heart.

Of 21 persons who were not examined until four to nine years after primary infection, 6 (28.6 per cent) revealed the presence of cardiovascular syphilis. Two of these suffered from aortic insufficiency and one from aneurysm. Symptoms were present in 3 of the 6.

Among 37 persons who were not examined until ten to nineteen years after the primary lesion, 21 (56.8 per cent) exhibited evidence of cardiovascular syphilis. Symptoms appeared in 51.3 per cent of these. Heart failure occurred in 2 patients, in both of whom aneurysm or aortic insufficiency was present.

In a group first observed from twenty to twenty-nine years after infection, 77.8 per cent exhibited signs of syphilitic heart disease; 40 per cent presented either aortic insufficiency or aneurysm. Symptoms were present in 78 per cent.

Of 17 persons who were first examined thirty or more years after infection, 15 revealed the presence of cardiovascular syphilis, and 7 either those of aortic insufficiency or of aneurysm; three quarters of them complained of cardiac symptoms.

Heart failure occurred only in those patients in whom aortic insufficiency, aneurysm or involvement of a coronary artery developed.

There were significant changes in the electrocardiograms within ten years after the appearance of the chancre in only 10.4 per cent. No changes were found that could be considered characteristic of the condition.

A case is reported of a patient whose condition was diagnosed as syphilitic disease of a coronary artery, who died within two years after the occurrence of the chancre. Postmortem examination confirmed the diagnosis.

CONCLUSIONS

1. Syphilis of the aorta can be recognized much earlier than in the past. In order to discover its presence it is necessary that every syphilitic patient be examined regularly by methods used in making a diagnosis of cardiovascular disease. These examinations should be repeated once in six months or once a year.

2. Roentgenograms and fluoroscopic examination provide the most reliable means of deciding whether abnormality of the aorta is present in early syphilis.

3. Heart failure occurs only in those patients in whom syphilitic involvement has passed beyond the stage of simple aortitis. In the patients studied myocardial failure appeared only after the development of aortic insufficiency, aneurysm or narrowing of the coronary arteries. Multiple gummas may be regarded as a cause of heart failure, but this condition was not encountered in this study. It is well known that these four manifestations are late lesions. Symptoms of heart failure usually prompt patients to seek relief in clinics for cardiac disease. Since these tend to occur late in cardiovascular syphilis and since no special routine effort has been made in the past to examine syphilitic patients for evidence of cardiovascular disease, the discovery of aortitis has been delayed. It is probably not true that syphilitic aortitis is a late lesion occurring, on the average, twenty years after the occurrence of the chancre. It is our opinion that involvement of the aorta begins soon after the chancre has appeared and that, in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination.

CONFUSING CLINICAL MANIFESTATIONS OF MALIGNANT RENAL NEOPLASMS

C. D. CREEVY, M.D.
MINNEAPOLIS

Malignant renal tumors should be classed with syphilis and tuberculosis as among the great mimics encountered in clinical medicine. By direct pressure, by necrosis or hemorrhage, by extension or by metastasis they can reproduce the clinical appearances of an amazing variety of disorders. This fact is often mentioned but rarely emphasized in discussions of renal neoplasms. My attention was first attracted to this fact by 2 cases in which fever was a prominent feature.[1] Study of the cases of renal tumor at the University Hospitals and in the department of pathology of the University of Minnesota showed that in many cases the tumor had mimicked some other disease, particularly at the time of onset of symptoms; hence further investigation seemed advisable. With this end in view a group of 92 cases was studied.

NOMENCLATURE

It is difficult to discuss neoplasms of the kidney without becoming involved with their nomenclature. For the sake of clarity this paper deals only with the malignant tumors of the renal cortex which are variously known as Grawitz tumors, hypernephroma (Birch-Hirschfeld [2]), nephroma (Bell [3]) or carcinoma (Wilson [4]). It is my opinion that these terms are synonymous and that arguments as to the propriety of one name as opposed to that of the others are fruitless.

USUAL SYMPTOMS

It is probably desirable at this point to review briefly the usual clinical picture of neoplasm of the kidney. The classic triad of symptoms—pain, tumor and hematuria—is firmly fixed in the mind of every

From the Division of Urology of the Department of Surgery, University of Minnesota Medical School.

1. Creevy, C. D.: Pyrexia in Malignant Nephroma (Hypernephroma), J. A. M. A. **92**:1256 (April 13) 1929.

2. Birch-Hirschfeld, F. V.: Beiträge zur pathologischen Anatomie der Nierengeschwülste, Beitr. z. path. Anat. u. z. allg. Path. **24**:343, 1898.

3. Bell, E. T.: A Textbook of Pathology, Philadelphia, Lea & Febiger, 1930, p. 262.

4. Wilson, L. B., and Willis, B. C.: A Comparative Study of the Histology of the So-Called Hypernephromata and the Embryology of the Nephridial and the Adrenal Tissues, J. M. Research **24**:73, 1911.

medical student, probably because of the attractive adjective "classic," in spite of the fact that nearly every writer on the subject, particularly Braasch,[5] has been at some pains to point out that the three are present *together* only late in the course of the disease, long after the diagnosis should have been made.

Hematuria is usually the most striking of the typical symptoms, and it is the most frequent (43 per cent of 367 cases of Judd and Hand [6]). The same authors obtained a history of pain in 37 per cent and of tumor as the initial symptom in but 14 per cent of their group. The presence of any one of these symptoms in a person at the stage of life regarded as the cancer age demands a thorough urologic study. In the last analysis the pyelogram is the only basis on which the diagnosis can be made with reasonable certainty; it should be obtained at a stage at which the symptoms are suggestive or but faintly suspicious. Only then is it possible to take advantage of the notoriously slow growth and late metastases which so many renal tumors exhibit. Even when these precautions are observed a considerable number of cases of renal tumor will inevitably be missed until after metastases have appeared because in many instances the latter occur before the primary tumor is large enough to cause any symptoms whatever.

CONDITIONS RESPONSIBLE FOR CONFUSION

Certain characteristics of the malignant renal neoplasm are responsible for the confusing picture which it sometimes produces. First among these is the tendency of such a neoplasm to grow very slowly. Kraft [7] had a patient whose history could be traced back for forty years; the tumor showed areas of cystic degeneration. Israel [8] said that a history of twenty years' duration could often be elicited. One of Ljunggren's [9] patients had had a palpable tumor for thirty years, and in Arkin's [10] case the growth was known to have existed for sixteen years; at operation it was calcified and partly ossified; nevertheless there was a prompt local recurrence. Further evidence of the slow growth of malignant renal neoplasms is found in the number of patients

5. Braasch, W. F.: Clinical Data on Malignant Renal Tumors, J. A. M. A. **60**:274 (Jan. 25) 1913.

6. Judd, E. S., and Hand, J. R.: Hypernephroma, J. Urol. **22**:10, 1929.

7. Kraft, S.: Selbstheilung des Hypernephroms, Ztschr. f. urol. Chir. **5**:16, 1920.

8. Israel, J.: Ueber einige neue Erfahrungen auf dem Gebiete der Nierenchirurgie, Deutsche med. Wchnschr. **22**:345, 1896.

9. Ljunggren, E.: Studien über Klinik und Prognose der Grawitzschen Nierentumoren, Acta chir. Scandinav. (supp. 16) **66**:1, 1930.

10. Arkin, A.: Calcified Hypernephroma of the Kidney, Surg., Gynec. & Obst. **43**:155, 1926.

in whom metastases have developed years after the original tumor had been removed. A notable example is the case of Albrecht [11] in which a metastasis developed in the scapula four years after nephrectomy. It was removed, and the patient was still living nine years after the second, and thirteen years after the first, operation. As no local symptoms are produced until the renal pelvis, its capsule or adjacent organs are invaded, it is natural that such a tumor should remain symptomless for a long time.

This tendency toward slow, progressive invasion is of importance in view of the situation of the kidneys, since because of it a malignant renal tumor may simulate a primary lesion of the bowel, stomach, biliary tract or spleen.

A third characteristic which is often confusing is the extensive manner in which the tumor may metastasize. As Lehmann [12] has pointed out, the spread may take place either in an antegrade or in a retrograde fashion both by way of the venous system and via the lymphatics. Metastases from these neoplasms have been found in nearly every organ of the body. The percentage of cases in which metastasis is the first sign of illness is difficult to determine, but Deuticke [13] found it to be 9 and Israel 50 per cent.

PYELOGRAPHIC APPEARANCE OF RENAL NEOPLASM

The deformity as revealed in the pyelogram is usually characteristic, although it may at times be difficult to recognize. According to Braasch, five characteristic changes are noted, namely: (1) elongation of one or more calices or of the pelvis; (2) encroachment on the pelvic lumen, causing flattening of the general pelvic outline, narrowing of the individual calices, obliteration of the true pelvis, obliteration of one or more calices or complete occlusion at or near the ureteropelvic juncture; (3) secondary pyelectasis; (4) abnormal position of the renal pelvis, and (5) deformity at the ureteropelvic juncture and upper portion of the ureter.

These changes vary markedly in extent. Probably the earliest type of recognizable change is exemplified in figure 1, a roentgenogram of an adenoma of the kidney, 2.5 cm. in diameter, which had just begun to invade a minor calix. Figure 2 shows the typical "spider-leg" deformity. Figure 3 illustrates an unusual change: multiple filling defects due to nodular intrapelvic projections of the tumor.

11. Albrecht, P.: Beiträge zur Klinik und pathologischen Anatomie der malignen Hypernephrome, Arch. f. klin. Chir. **77**:1073, 1905.

12. Lehmann, W.: Hypernephrommetastasen des Skelettsystems, Arch. f. klin. Chir. **170**:331, 1932.

13. Deuticke, P.: Nierentumoren, Deutsche Ztschr. f. Chir. **231**:767, 1931.

CONDITIONS SIMULATED BY RENAL NEOPLASMS

Renal neoplasms and their metastases mimic such a large and unrelated variety of disorders that any orderly classification is difficult. For convenience, the following arrangement has been employed: (1) metastases to the osseous system, (2) metastases to the lungs and pleura, (3) metastases to the digestive tract, (4) metastases to the female genitalia, (5) metastases to the neck, (6) metastases to the skin, (7)

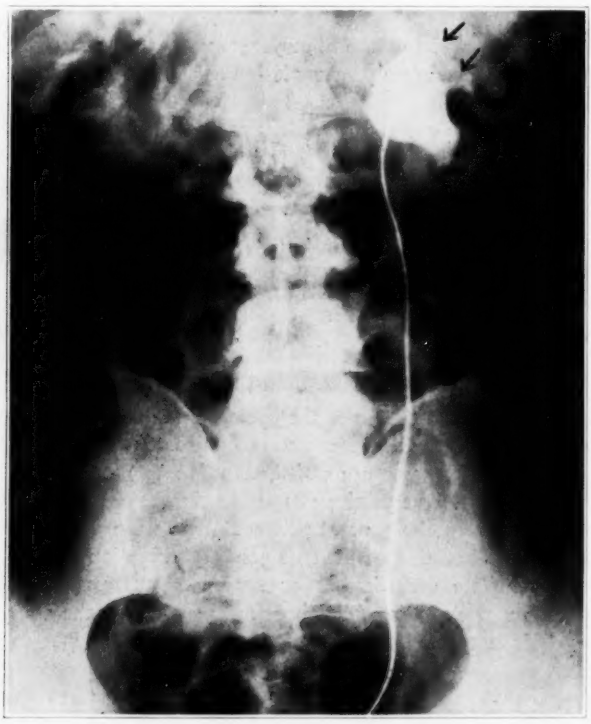

Fig. 1.—Early deformity from a renal neoplasm (adenoma).

metastases to the central nervous system, (8) metastases causing anemia, (9) metastases causing fever and (10) metastases simulating other disorders of the urinary tract. The osseous system is most often involved.

Metastases to the Osseous System.—Lehmann collected reports of 56 cases of bony metastases from the literature. He found that in 9 of these there were multiple metastases and therefore the condition was rather obviously metastatic; in 13 either at autopsy or by prolonged

survival after removal the metastatic growth was proved to be solitary, while in 34 it was solitary as far as could be ascertained clinically. Twenty-four metastases were in the flat and 23 in the long bones; they occurred in the skull, sternum, clavicle, vertebrae, scapula, humerus, ulna, femur, tibia and tarsus. It is difficult to ascertain from the protocols given by Lehmann in what percentage of cases the solitary metastatic tumor was mistaken for a primary lesion, but the number of instances in which the diagnosis was suspected only after removal

Fig. 2.—Typical deformity of the renal pelvis from a neoplasm.

and histologic examination of the metastatic deposit is rather high. In Schinz' [14] series of 10 cases, 3 were diagnosed correctly because of previous nephrectomy for hypernephroma, 3, after biopsy, and 3, only at autopsy. In 1 the metastatic growth was mistaken for a metastatic seminoma. In this case when the disease failed to respond to radiation therapy the diagnosis was changed to hypernephroma; this was later verified at autopsy. In the literature Schinz found that in 7 cases metastasis of hypernephroma to bone had been mistaken for osteogenic

14. Schinz, H. R., and Uehlinger, E.: Das Hypernephrom und seine Knochenmetastasierung, Acta radiol. **14**:56, 1933.

sarcoma; in 3, for tuberculosis, and in 1 each, for aneurysm of the aorta, metastasis from seminoma and primary giant cell tumor.

The most reliable guide to a correct diagnosis is the appearance of the metastasis as revealed by roentgen examination. This appearance, while often fairly typical, is rarely so characteristic as to permit a final conclusion without the aid of pyelograms. Schinz has described two typical and several atypical varieties. The chief features are destruction of bone without expansion, periosteal reaction or formation

Fig. 3.—Multiple filling defects due to a hypernephroma.

of new bone. The most easily recognized form presents a central oval defect, often with a pathologic fracture, in the diaphysis of a long bone. There is a similar picture in the flat bones which is equally characteristic and which Schinz called the "soap-bubble form." Less typical are ragged, oval areas of destruction with slight sclerosis at the margins. Occasionally such areas show sequestrums. Schinz observed one exceptionally puzzling case in which the lateral aspect of the femur was eroded and showed formation of new bone in the soft parts and a slight periosteal reaction which suggested a parosteal sarcoma.

To sum up, one suspects the diagnosis from the roentgen appearance but makes it definitely only from the urogram. The physical character of the metastatic tumor is usually confusing rather than helpful.

Metastases to the Lungs and Pleura.—Lesions in the lung less often cause confusion because by the time they become evident the primary tumor has usually attracted attention. However, Waser [15] reported the case of a patient who had been treated for pulmonary disease for five years before the true nature of the condition was recognized, and Vinson and Martin [16] made the diagnosis of metastasis after microscopic examination of a fragment of an apparently primary pulmonary tumor secured with the bronchoscope. The renal lesion was wholly symptomless.

The clinical appearance of a pulmonary metastasis is not typical unless the primary tumor has been discovered. There may be pain in the chest, cough and hemoptysis, but the lesion may be entirely symptomless. The physical findings are equivocal or absent as the metastasis may be so small or so placed as to escape detection. Thus dependence on roentgen examination is absolutely necessary. In roentgenograms metastases from renal tumor appear as single or multiple rounded areas of increased density which vary widely in size (fig. 4). They are rather sharply marginated and have smooth edges, but not to the degree seen in secondary deposits from teratoma of the testis. Similar lesions may be produced by osteogenic sarcoma and occasionally by carcinoma of the rectum or breast or by some other neoplasm. Thus again, roentgen examination of the metastatic lesion is suggestive only and must be verified by pyelographic studies.

Metastases to the Digestive Tract.—Two instances of metastasis to the tongue have been reported: one by Coennen and one by McKenzie and Waugh.[17] In the first the tumor of the base of the tongue and that of the kidney were both removed, and the patient was well five years later. In the second the patient died of generalized metastases, and the diagnosis was verified at autopsy.

Gastro-intestinal symptoms, chiefly postprandial epigastric distress, nausea and vomiting, are not uncommon in cases of surgical lesions of the kidney. In the majority of instances they are probably reflex in character, but in certain cases of malignant growth they are due to

15. Waser, G.: Schwere eigenartige Anaemie von hämolytischem Charakter bei nicht blutenden Hypernephrom, Folia haemat. **26**:45, 1920.

16. Vinson, P. P., and Martin, W. J.: Pulmonary Metastasis from Hypernephroma Diagnosed by Bronchoscopy, Arch. Otolaryng. **15**:368 (March) 1932.

17. McKenzie, D. W., and Waugh, T. R.: Cystadenoma pseudopapilliferum Malignum of the Kidney with Metastasis in the Tongue, J. Urol. **20**:121, 1927.

direct invasion of the stomach or bowel. Grohé [18] and Thierry [19] have reported instances of invasion of the pylorus by a tumor of the right kidney which produced an obstruction requiring gastro-enterostomy. The true nature of the lesion was recognized at autopsy. Thierry also described the case of a physician in whom an acute intestinal obstruction developed which at operation appeared to be due to a tumor of the splenic flexure of the colon. Recovery followed cecostomy, but the patient died of pneumonia following the surgical closure of the aperture.

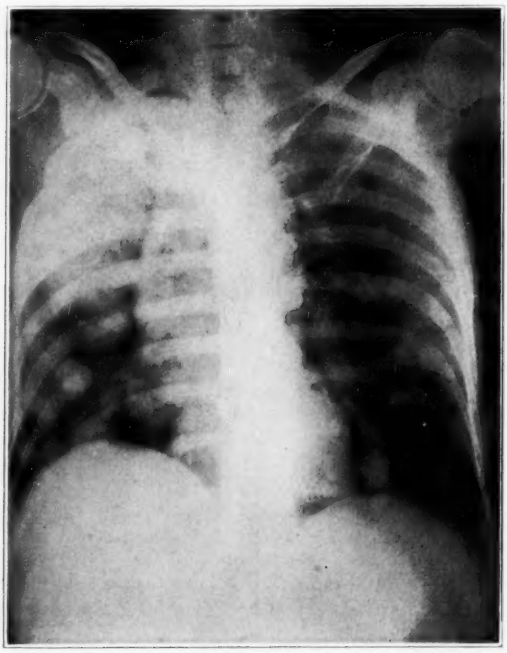

Fig. 4.—Pulmonary metastases.

Autopsy disclosed a malignant neoplasm in the left kidney with a spontaneous perirenal hemorrhage which had compressed the bowel. Direct invasion of the large bowel is not uncommon and may at times be amenable to resection and nephrectomy, as in a case described by Sugar.[20]

18. Grohé, J. B.: Unsere Nierentumoren in therapeutischer, klinischer, und pathologisch-anatomischer Beleuchtung, Deutsche Ztschr. f. Chir. **60**:1, 1901.

19. Thierry, H.: Beitrag zur Symptomatologie und Therapie des Hypernephroms, München. med. Wchnschr. **68**:638, 1921.

20. Sugar, H.: Renal Neoplasm with Resection of Involved Colon, J. Urol. **24**:487, 1930.

Scheele [21] and Albarran and Imbert [22] have observed jaundice from compression of the common bile duct. Garrow [23] had a patient who exhibited the typical symptoms of portal cirrhosis with weakness, gastrointestinal disturbances, pyrosis, ascites, edema and slight jaundice and in whom autopsy revealed a carcinoma of the right kidney which had occluded the renal vein and vena cava and invaded the regional glands.

Recognition of metastasis of the digestive tract is always difficult, particularly if the patient is first seen during an attack of intestinal obstruction; in such a case the diagnosis may be made at operation. In other situations correct diagnosis is largely a question of bearing in mind the possibility of renal tumor in atypical cases and of resorting to pyelography.

Metastases to the Female Genitalia.—The female genitalia may be involved and present confusing symptoms. Gellhorn [24] found in the literature 14 instances of metastasis to the vaginal wall, most of which were identified only after histologic examination. Usually the lesion is a circumscribed, nonulcerated, submucous nodule, which is easily enucleated and is attributed to retrograde metastasis from the renal vein along the ovarian vein. Gräfenburg found such a lesion in the introitus adjoining the clitoris.

Garceau [25] and Funccius [26] have each reported cases of metastasis to the ovaries, and Garceau mentioned one instance of metastasis to the uterus. In Carey's case the neoplasm simulated ectopic pregnancy because of hemorrhage about a low-lying renal tumor, but the condition was recognized cystoscopically.

Metastases to the Neck.—Occasionally a secondary deposit may appear in the neck, apparently propagated by way of the thoracic duct or supraclavicular glands (Deuticke, Israel, Claessen [27]). It is usually recognized by microscopic examination of excised tissue.

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26. Funccius: Ueber von versprengten Nebennierenkeimen ausgehende Tumoren beider Nieren kompliziert durch Hufeisenniere, Erlangen, Junge & Sohn, 1905.

27. Claessen, M.: Die Verbreitungswege des Hypernephroms und die Beeinflussung der Geschwulstbildung durch Traumen, Breslau, Bresl. Genossensch.-Buchdr., 1919.

Metastases to the Skin.—Metastatic nodules in the skin and subcutaneous tissues are not uncommon and present no difficulty because excision and examination are easily made, but a much less readily recognized lesion was described by Clairmont [28] and subsequently verified by Waser, Pleschner,[29] Deuticke and others. It consists of a peculiar bronzing of the skin, which involves the neck, the elbows, the areola of the nipples and the buccal and palatal mucosa and is due to the deposition of small, closely set dark flecks of pigment in the skin. There is a superficial resemblance to Addison's disease. Recognition depends on discovery of the lesion in the kidney.

Metastases to the Central Nervous System.—Occasionally the first symptom is referable to the central nervous system. The metastasis may mimic a neuritis from compression or invasion of a nerve trunk by metastatic nodules—as in the case of Berg [30] in which a metastasis in the ischium involved the sciatic nerve—or a paraplegia secondary to compression of the spinal cord by vertebral metastasis (Deuticke, Garrow and Keenan). Intracranial involvement may mimic a primary tumor of the brain (Hoffman,[31] Huggins [32]).

Metastases Causing Anemia.—Occasionally a case has been reported in which the symptoms resembled closely those of so-called primary anemia. In the case of Waser there was pigmentation of the skin, and the presence of pernicious anemia was suspected. After a period of observation a renal tumor was found. It is interesting that there had been no hematuria; the origin of the anemia was thus left in doubt. It is possible that bleeding into the tumor was responsible, since the hemoglobin content of the blood did not fall below 60 per cent.

Metastases Causing Fever.—I have recently reviewed the subject of fever of noninfectious origin in cases of malignant tumors of the kidney. The condition was first recognized by Stetter [33] and was found by Israel in 18.2 per cent of all the cases he observed. He distinguished initial, intercurrent and terminal types, dividing each into hectic, recurrent and hematuric, and suggested that when infection was absent the elevation of temperature was due to the formation in the tumor of a

28. Clairmont, P.: Beiträge zur Nierenchirurgie, Arch. f. klin. Chir. **79**:667, 1906.

29. Pleschner, H. G.: Beiträge zur Klinik und pathologischen Anatomie der malignen Hypernephrome, Ztschr. f. urol. Chir. **1**:309, 1913.

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31. Hoffman: Hypernephrommetastasen, Zentralbl. f. Chir. **34**:82, 1907.

32. Huggins, C. B.: Hypernephroma Without Symptoms or Signs, S. Clin. North America **9**:382, 1929.

33. Stetter: Demonstration eines exstirpirten Pyloruscarcinomoms und einer extirpirten carcinomatösen Niere, Verhandl. d. deutsch. Gesellsch. f. Chir. **16**:36, 1887.

pyrogenic substance. While the source of the fever may be obvious it may, as in Nicholson's [34] case, be the only symptom and cause extreme difficulty in diagnosis.

Metastases Simulating Other Disorders of the Urinary Tract.—Occasionally, even though the tumor produces symptoms directly referable to the urinary tract, the diagnosis may be obscure because of the atypical nature of the symptoms, especially when no tumor is palpable. Since, as Ljunggren has pointed out, a tumor of the kidney in order to be palpable must be at least as large as a man's fist—unless it is in the anterior surface of the lower pole or unless the patient is emaciated—such confusion is potentially frequent. Clots of blood may cause retention of urine and produce symptoms similar to those of tumor of the bladder or of obstruction of the vesical neck (Pleschner). An inexperienced cystoscopist may mistake the clots for a neoplasm in the bladder.

Squier [35] reported two instances in which shadows in the roentgenograms of patients with renal colic and hematuria were mistakenly regarded as being caused by stones when they actually represented areas of calcification in a tumor. In a third instance the shadows were due to stones coexisting with a neoplasm. Crane [36] had a patient with a small and previously symptomless tumor beneath the capsule which was recognized only because it caused a perirenal hematoma which led to operation.

REVIEW OF CASES

General Considerations.—Ninety-two cases of malignant neoplasms of the parenchyma of the kidney have been reviewed in an effort to ascertain how frequently the presenting symptoms were such as to cause confusion with symptoms of some other lesion. Forty-six of these cases were found in the autopsy material of the Department of Pathology at the University of Minnesota and 46 in the clinical records of the University Hospitals. In assembling the material 30 cases of tumors were rejected because they represented only incidental findings in patients who died of other, wholly unrelated, conditions. These tumors were small, encapsulated and located at a distance from the calices and pelvis and played no part in causing the patient's symptoms or death. No cases are included in which reasonable doubt existed as to the existence of a renal tumor or of its rôle in producing the symptoms of which the patient complained.

34. Nicholson, D.: Fever with Renal Carcinoma, Arch. Path. **3**:393, 1927.

35. Squier, J. B.: Neoplasms of the Kidney and Ureter, Boston M. & S. J. **161**:547, 1909.

36. Crane, W. J.: Renal Tumor; Unusual Complication Leading to Early Diagnosis, J. Urol. **22**:535, 1929.

The impression produced by a survey of the 92 cases is not a pleasant one. In the autopsy series, since the patients died of renal tumor, the incidence of metastases was naturally high (43 of 46 cases, or 93.5 per cent). It was surprising to learn that there had been demonstrable secondary deposits in 35 (76 per cent) of the cases in the clinical series. This figure is especially striking when one considers that before 1925 roentgen examinations of the chest were not made as a routine; hence the true incidence of metastasis must be still higher.

TABLE 1.—*Location of Secondary Lesions in Seventy-Eight Cases of Renal Neoplasm in a Group of Ninety-Two Cases*

Location	Number of Lesions		
	Autopsy Series	Clinical Series	Total Series
Bones	23	28	51
Lungs	28	12	40
Liver	16	3	19
Regional glands	13	3	16
Opposite kidney	11	1	12
Renal vein	7	4	11
Vena cava	7	..	7
Adrenal gland	7	..	7
Brain	5	1	6
Pancreas	4	1	5
Pleura	3	2	5
Diaphragm	3	1	4
Peritoneum	2	2	4
Colon	3	..	3
Omentum	2	1	3
Pericardium	2	1	3
Small bowel	2	1	3
Gallbladder	2	..	2
Supraclavicular glands	..	2	2
Mediastinal glands	2	..	2
Mesenteric glands	2	..	2
Neck	1	1	2
Heart	2	..	2
Spleen	2	..	2
Stomach	..	1	1
Ovarian vein	1	..	1
Iliac vein	1	..	1
Femoral vein	1	..	1
Skin	1	..	1
Buttock	1	..	1
Perineum (male)	1	..	1
Urethra	1	..	1
Testis	..	1	1
Epididymis	1	..	1
Ureter	1	..	1
Bladder	..	1	1
Total	158	67	225

The interesting feature in both series of cases for the purposes of this paper is the fact that the symptom which caused the patient to consult a physician did not in any way suggest the existence of a renal neoplasm as a causative factor in 41.3 per cent of the whole group. The incidence of atypical cases was, for obvious reasons, somewhat higher in the autopsy series (50 per cent) than in the clinical series (32.6 per cent) since autopsy is more often performed in confusing or obscure than in clearcut cases.

It seems worth while to digress in order to enumerate the astonishing number of organs in which metastases or extensions were found (table 1). Thirty-six organs or systems were involved a total of 225 times. As is usual in most series, the bones (table 2) and the lungs were most frequently affected.

Certain discrepancies in the table require explanation. It will be noted that involvement of the pericardium occurred once in the clinical series. As a matter of fact, the condition was found at autopsy; in 12 of the cases in the clinical series necropsy was performed, but these cases have been classed with their original series. The greater incidence of metastasis to the other kidney and to the renal vein, vena cava and regional glands observed in the necropsy series is due to the greater accessibility of these structures for pathologic examination; the more frequent involvement of the humerus as revealed clinically is probably

TABLE 2.—*Distribution of Fifty-One Metastatic Lesions of Bone*

Location	Number of Lesions		
	Autopsy Series	Clinical Series	Total Series
Spine	7	6	13
Pelvis	4	4	8
Ribs	4	3	7
Humerus	..	6	6
Femur	3	3	6
Skull	2	3	5
Mandible	..	1	1
Clavicle	..	1	1
Sternum	1	..	1
Scapula	..	1	1
Tibia	1	..	1
Fibula	1	..	1
Total	23	28	51

due to the pathologist's reluctance to mutilate the body unnecessarily. Unquestionably necropsy or roentgen examination of all the bones as a routine procedure would increase enormously the number of cases in which bony metastases are recognized.

ATYPICAL CASES

To return to the original problem of the cases presenting confusing or atypical symptoms at the onset, tables 3 and 4 show what a variety of pathologic conditions have been simulated. Here again bony metastases head the list (16 of 38 cases), and pulmonary metastases are a fairly close second. In the autopsy series, pain in the spine (most often in the lumbar or sacral region) frequently constituted the patient's first complaint; not uncommonly this symptom occurred after a slight trauma which probably called attention to a preexisting but hitherto painless lesion. In the clinical series a secondary deposit in the humerus was most often the first sign of illness. In all, four patients sustained

pathologic fractures of that bone after slight injuries (fig. 5); in only one had a tumor in the bone been noted first. None had any of the classic symptoms of renal tumor, and the presence of such a tumor was demonstrated by pyelography.

The literature states that metastases to bone often pulsate; this was not true in any of the cases observed in the clinical series; the tumor was palpable in only 3 and it was solid in all. Although instances of solitary bony metastasis are often reported, in all the cases in this

TABLE 3.—*Conditions Simulated by the Metastasis or Extension of Renal Neoplasms*

Nature	Number of Autopsy Series	Number of Clinical Series	Number of Total Series
Tumor of the bones	10	6	16
Spine	5	1	
Humerus	..	4	
Femur	2	..	
Pelvis	1	..	
Tibia	1	..	
Skull	1	..	
Clavicle	..	1	
Pulmonary disease	5	4	9
Tumor of the brain	2	..	2
Encephalitis	..	1	1
Myelitis	1	..	1
Neuritis of the brachial plexus	1	..	1
Tumor of the neck	1	1	2
Portal cirrhosis	1	2	3
Carcinoma of the stomach	..	1	1
Intestinal obstruction	1	..	1
Perlurethral abscess	1	..	1
Total	23	15	38

TABLE 4.—*Conditions Simulated by the Tumor Itself* *

Nature	Incidence
Tumor of the bladder	2
Nephrolithiasis	1
Ovarian cyst	1
Total	4

* All the figures given in this table are from the clinical series.

group the metastases were multiple. As was pointed out earlier, the diagnosis usually depended on the suspicion as to the existence of the osseous lesion as aroused by the roentgenograms and was verified by pyelography. In one case in the autopsy series the diagnosis was made during life by examination of material curetted from what appeared to be a cyst in a bone, and in another it was made only at autopsy, the patient having died shortly after he sustained a pathologic fracture of the femoral neck.

One may say that the presence of metastatic tumor of the kidney should be suspected in any atypical, destructive lesion of bone in a middle-aged or elderly patient, especially if the lesions are multiple;

the metastasis as well as the primary tumor may be impalpable so that in many instances one is completely dependent on the roentgen examination. In suitable cases biopsy may be employed, particularly if the lesion is in the subcutaneous bones. Nevertheless, in a few cases the condition will not be recognized except at autopsy.

In 9 of the 38 confusing cases the patient first sought advice because of symptoms referable to the lungs, usually in the form of cough, pain in the chest and hemoptysis. Two cases presented particular difficulty. In 1 the diagnosis was not made until typical lobar pneumonia failed to resolve; roentgen studies then showed typical metastases, and subsequent pyelography established the diagnosis. In another, the condition

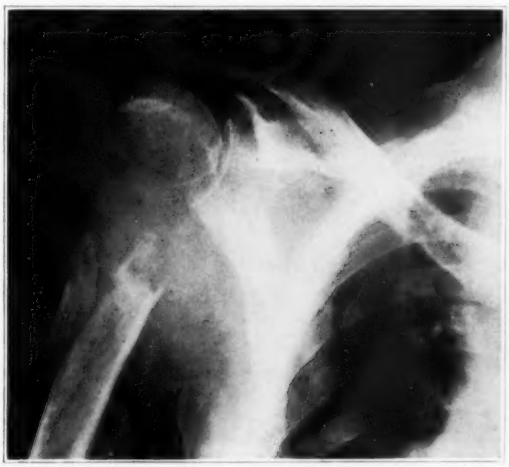

Fig. 5.—Metastases to the humerus with pathologic fracture.

developed in a patient discharged a few years before from a sanatorium where tubercle bacilli had been found in the sputum. In the remainder the complaints already noted were present, and the condition was recognized by roentgen examination.

In 2 cases in which autopsy was performed there were symptoms of an unlocalizable lesion of the brain and, in the complete absence of urinary symptoms or palpable tumors, the condition was not recognized during life. There is nothing characteristic about these cases. In 1 case in the clinical series there was a history suggestive of encephalitis in that the patient often fell asleep at the dinner table; he complained of stiffness of the neck and back and of generalized headaches. The absence of definite findings led the neurologist to suspect the presence of an abscess of the brain or a tumor, possibly, because of the atypical

character of the findings, a metastatic hypernephroma. Urologic consultation was asked, but because the patient was obviously moribund cystoscopic examination was not made; intravenous urograms were unsatisfactory. Autopsy showed extensive cerebral metastases.

In this case again the diagnosis depended on suspicion aroused by atypical cases and verified by pyelography. It may be noted at this point that intravenous urography has not been wholly satisfactory in establishing a diagnosis of renal tumor at the University Hospitals. Retrograde pyelograms have been required in nearly every case because the impairment of renal function by the tumor has prevented adequate visualization of the diseased kidney.

In another instance paraplegia with sphincteric incontinence developed in a middle-aged patient when he fell from a truck and struck his spine. Several months later roentgen studies revealed metastases in the lumbar portion of the spine. While there is a considerable amount of speculation in the literature as to the relationship between trauma and the development of metastases, especially in bone, it is futile to theorize here. It seems logical to suppose that there was a hemorrhage into a metastasis in the cord at the time of the injury, since roentgenograms made shortly thereafter showed nothing abnormal. This was a case of the type which usually continue to escape diagnosis until necropsy, since there were no symptoms to identify either the primary tumor or the metastases.

Another patient presented neuritic symptoms referable to the brachial plexus. Sufficient details are not available as to physical findings.

Among the obscure cases must be listed that of a man, aged 62, who had been admitted to the hospital with vague abdominal discomfort and intermittent edema of the ankles and who was dismissed after considerable study with a diagnosis of possible malignant tumor of undetermined location. He returned seven years later with a slowly growing mass beneath the lower end of the left sternocleidomastoid muscle. The tumor was as large as an apple and was hard, nodular and fixed. The right kidney was palpable, and the superficial abdominal veins on the right side were distended; they transported blood upward. The pyelogram of the right kidney showed a typical renal neoplasm. Biopsy of the mass in the neck showed "hypernephroma" (fig. 6).

A similar case was found in the autopsy series. A man, aged 83, had complained of a cough, dyspnea and hemoptysis of six months' duration; these symptoms were complicated two months before hospitalization by evidence of a tumor in the lower anterior part of the neck on the left side. The patient died shortly after aspiration of the left pleural cavity; autopsy revealed a small hypernephroma on the left side. It had metastasized to the lungs, regional glands and left supraclavicular lymph nodes.

In 2 cases renal tumors mimicked hepatic cirrhosis and disease of the biliary tract. In 1 of these, a woman aged 30 had noted weakness, dyspnea, cough and edema of the ankles for four years, and two years before admission chills, fever, pain in the right upper abdominal quadrant and jaundice had developed. An abdominal exploration in another hospital had shown apparent cirrhosis of the liver and chronic cholecystitis. After cholecystostomy there was temporary improvement, but two years later mild jaundice, ascites and edema developed. The urine was normal. The patient died shortly after admission to the hospital, and the necropsy demonstrated that the supposed cirrhosis was due to

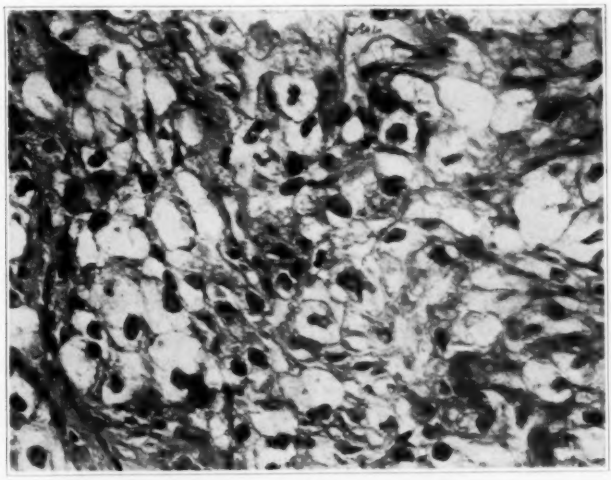

Fig. 6.—Microscopic appearance of a hypernephroma metastasizing to the neck.

multiple nodular tumors secondary to a carcinoma of the right kidney which had extended into the renal vein and vena cava.

Two cases so similar to the last that they need not be described in detail were found in the autopsy series.

One patient, aged 55, in the clinical series presented a typical picture of carcinoma of the stomach, with a recent loss of weight of 25 pounds (11.3 Kg.), anorexia, pain in the epigastric region after eating and vomiting. There was an ill defined mass in the left upper quadrant of the abdomen, and severe anemia was present; the urine contained a few white blood cells. However, ordinary roentgenograms of the abdomen showed erosion of the left margin of the upper two lumbar vertebrae (fig. 7); roentgenograms of the gastro-intestinal tract showed only displacement of the stomach and colon, and a pyelogram of the left kidney showed conditions typical of renal neoplasm. The patient

failed rapidly and died. The digestive disturbances could probably be explained by invasion of the ileum which was found post mortem.

In another case in the autopsy series symptoms of a gastro-intestinal lesion were present in a patient who sought aid for a typical acute intestinal obstruction coming on with few premonitory symptoms. Exploration established the fact that the obstruction was due to infiltration of the splenic flexure of the colon by a growth in the left kidney. The

Fig. 7.—Erosion of the bodies of the vertebrae by a hypernephroma of the left kidney.

patient died in spite of a colostomy for the obstruction, and autopsy verified the diagnosis.

Only once in the whole group was there confusion between a renal neoplasm and a lesion of the female genitalia. A woman, aged 66, had twice received radium for metrorrhagia before a smooth, rounded, freely movable mass was noted in the right lower quadrant of the abdomen; it was palpable also on pelvic examination. The urine was normal. A diagnosis of ovarian cyst with uterine bleeding was made, but a carcinoma in the lower pole of a movable, ptotic kidney was found at operation and removed through a median subumbilical incision.

In 4 cases a renal neoplasm was mistaken for another type of lesion of the urinary tract.

The first of these was in a man, aged 53, who had had renal colic on the right side and hematuria and had passed stones at frequent intervals for two years. An ordinary roentgenogram of the urinary tract showed shadows in the region of the right kidney; on pyelography these shadows appeared to be included in the renal pelvis, which also contained many irregular shadows thought to be soft stones (fig. 3). At operation, however, there was found a large hypernephroma which invaded the pelvis, producing the irregular shadows; two stones were also present. In this case the error was one of interpretation of the pyelogram, since the symptoms were undoubtedly due to nephrolithiasis.

In two other cases a diagnosis of tumor of the bladder had been based on cystoscopy by the family physician. In each there was a history only of painless hematuria, culminating in one case in urinary retention due to the formation of a clot. In neither was there any palpable mass, and in both cystoscopy demonstrated renal bleeding, and pyelography, renal neoplasms. These cases, of course, represent confusion of blood clots with vesical neoplasms, an error easily avoided if a biopsy is made on tissue removed by means of the cystoscope, since an attempt to secure tissue makes the nature of the mass in the bladder clear.

In one case in which the primary tumor was known to exist a metastasis to the bladder was suspected at cystoscopy, but this was not verified by microscopic examination. The ureteral metastasis in the autopsy series was an incidental finding.

In the final case to be mentioned (from the autopsy series) a man, aged 37, suffered from backache in the region of the sacrum and from low grade, intermittent fever for several months before a swelling of the left side of the scrotum and urinary retention developed simultaneously. Catheterization was followed by the development of a tender, hard mass in the penoscrotal angle. It was thought to be a periurethral abscess, but incision showed the mass to be solid; on microscopic examination it suggested a necrotic adenocarcinoma. The patient died twenty-four hours after amputation of the penis, and necropsy disclosed a hypernephroma of the left kidney with metastasis to the lungs, liver, regional glands and left epididymis.

This is a case of the type which defies clinical recognition.

COMMENT

There is no doubt that a fairly high percentage of the cases of renal neoplasm will continue to escape recognition until late in their course, not merely because patients are prone to delay medical consultation and

because the disease often produces syndromes difficult to identify, but chiefly by reason of the fact that the first symptom to attract the patient's attention is so often due, not to the tumor itself, but to a metastasis or local extension. This was the case in 32.6 per cent of the cases in the clinical series, in 50 per cent of those in the autopsy series and in 41 per cent of those in the whole group—a disconcertingly high proportion.

This is a situation which cannot at present be fully met in any practicable manner. To be sure, a painstaking eliciting of the history would perhaps have revealed facts which would have brought up the question of renal neoplasm, particularly if there was a hematuria which had been forgotten by the patient, or a brief attack of renal colic. A more careful physical examination in obscure cases may be helpful, but it is of uncertain value, since many normal kidneys are palpable and since many large tumors escape detection. The key to the whole problem lies in considering the possibility of a malignant renal tumor in every case of an obscure ailment, particularly in cases of tumors of the bone, of unusual lesions of the lungs, gastro-intestinal tract and nervous system and of obscure fever or anemia. In the investigation of such conditions intravenous urography is a valuable diagnostic aid because it spares the patient the discomfort of a cystoscopy. It is true that it may often impede a positive diagnosis because the affected kidney fails to excrete the dye; nevertheless such an event focuses attention on the kidney and may lead to a positive diagnosis with the aid of a retrograde pyelogram. On the other hand, if two normally functioning and normally formed pelves are demonstrated, the possibility of renal neoplasm is rather definitely excluded.

The question cannot be discussed without a mention of solitary metastasis, chiefly because there are on record several instances in which microscopic examination of a supposedly primary tumor after its excision led to the recognition and removal of a hypernephroma and to the survival of the patient for periods up to thirteen years. There was no case of solitary metastasis in this group; however, Lehmann found that in 13 of 56 cases of metastatic hypernephromas of bone recorded in the literature the metastasis was solitary as shown either at autopsy or by prolonged survival of the patient after operation; in 34 additional cases it was solitary as shown clinically. While it should be pointed out that most of this material comes from reports suggesting the advisability of surgical intervention and hence does not represent a true picture of actual conditions, instances of solitary metastasis apparently do occur. If, after painstaking search, a metastatic tumor of the bone proves to be solitary its removal together with that of the primary lesion may be considered.

It must be admitted that the questions involved here are, in a sense, largely academic, since once it has been determined that one of these obscure disturbances is due to a primary malignant tumor of the kidney there is usually little hope of cure except in instances in which another disease of the urinary tract has been simulated. However, the accurate identification of these cases will save many unnecessary operations and much futile treatment and will permit a more accurate prognosis.

SUMMARY AND CONCLUSIONS

The first symptom of a malignant neoplasm of the kidney is often due, not to the primary tumor itself, but to a distant metastasis or to extension to a neighboring organ. This was true in 32.6 per cent of 46 clinical cases and in 50 per cent of 46 autopsy cases herein reviewed.

Such a metastasis or extension may mimic a neoplasm of the bone, pulmonary disease, a lesion of the brain, spinal cord or peripheral nerves, cirrhosis of the liver, a lesion of the stomach or colon or a tumor of the neck, or it may cause unexplained anemia, fever or cutaneous lesions. It may also cause confusion with other diseases of the urinary tract (renal stones, vesical tumors, periurethral abscess) or be masked by them (stones). The primary tumor may be mistaken for an ovarian cyst.

Confusion may at times be avoided by a painstaking eliciting of the history and by a careful physical examination; the lesions are best recognized in obscure cases if one bears in mind the possibility of a renal tumor and excludes that diagnosis by intravenous urograms supplemented, as is often necessary, by retrograde pyelograms.

There was no instance of solitary bony metastasis in this group, although such a metastasis occasionally occurs and may be amenable to surgical intervention.

Thirty-six different organs—counting the bones as one organ system—were involved by metastasis in 92 cases of malignant renal neoplasm here reviewed. Twelve different bones were affected.

Since this article was written, three additional unusual instances of hypernephroma have been seen at the University Hospitals.

The first was the case of a woman, aged 39, who had been treated for several months in the outpatient department because of low grade fever, occasional rigors, generalized pain, and anemia (the hemoglobin was from 43 to 55 per cent). Because of a history of exposure, an agglutination titer at first of 1:80 and later of 1:320 for Brucella abortus and a positive Foshay cutaneous test, a diagnosis of undulant fever was made. Treatment with Foshay's vaccine produced no improvement, but chills, fever and loss of weight continued. The patient died after a series of convulsive seizures recurring over a period of several weeks.

Autopsy showed a necrotic hypernephroma of the right kidney without metastasis. The brain and meninges were normal. There was some proliferation of the reticulo-endothelial cells of the liver and spleen.

It is interesting but rather fruitless to speculate as to the relative rôles of the renal neoplasm and the undulant fever in producing the fatal outcome.

The second case was that of a man, aged 64, with a history of cough of three years' duration without impairment of the general health. Two months before admission there was hemoptysis followed by the coughing up of a "piece of flesh." This was examined by a pathologist who said that it resembled a papilloma. Later another piece was coughed up, and the tissue was diagnosed as carcinoma of undetermined origin. Roentgen examination of the chest showed an irregular infiltration extending from the hilus of the right lung and suggesting a bronchogenic carcinoma. Bronchoscopy was made with negative results. The patient then had hematuria for the first time and was hospitalized for pyelography. There had never been any other urinary symptoms. The pyelograms showed a typical neoplasm of the right kidney. Reexamination of the sections of the second coughed up specimen showed it to have an appearance consistent with that of hypernephroma.

The third case was that of a man, aged 49, who consulted his physician in April 1934 because of loss of weight and strength. Examination showed pleural effusion on the left side, and the patient was sent to a sanatorium. He was discharged after five months, much improved and classed as nontuberculous. Three months later weakness of the left arm developed, which was followed by attacks of jacksonian epilepsy. The patient was then admitted to the University Hospital; a tumor of the right frontal lobe was suspected. Roentgenograms of the lungs demonstrated nodular metastases. The right kidney was found to be nodular and enlarged; excretory urography showed a picture typical of renal neoplasm.

ALTERATIONS OF THE ELECTROCARDIOGRAM IN DISEASES OF THE PERICARDIUM

EDWARD H. SCHWAB, M.D.
AND
GEORGE HERRMANN, M.D.
GALVESTON, TEXAS

In the voluminous literature on electrocardiography comparatively little space has been devoted to the electrocardiographic findings in diseases of the pericardium. The mechanism of the production of these alterations has interested us. Recently [1] attention has been directed to the similarity of the changes occurring in the RS-T segment of the electrocardiogram in cases of pericardial involvement with an accumulation of fluid in the sac and those seen in the early stages of acute closure of a coronary artery. We have been able to find only one reference [2] in the clinical literature to the changes in the T wave occurring in diseases of the pericardium. Serial electrocardiographic studies, such as we have made, have not been previously carried out in the various stages of pericardial involvement, and this accounts, in a measure, for the paucity of data concerning the abnormalities appearing during inflammation, effusion, reabsorption and healing of the processes. We have been able to show that the electrocardiographic analogy that exists between acute pericardial processes and coronary thrombosis with cardiac infarction not only occurs at the time of the acute stage but continues through the periods of healing and repair. Elevations of the RS-T sector or "high take-offs" occurring in cases of acute pericardial effusion and hemopericardium are followed by progressive changes in the T wave which simulate, in most respects, the changes occurring in cases of acute and healing myocardial infarctions. At this point it is to be emphasized that similar abnormalities of the T wave may occur in cases of acute fibrinous pericarditis, irrespective of etiology, without an accompanying effusion and without preceding changes in the RS-T segment. As the clinical pictures of pericardial processes and coronary thrombosis with myocardial infarction may also so closely mimic one another, it behooves one to bend every effort to establish

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From the Department of the Practice of Medicine, School of Medicine, University of Texas, and the John Sealy Hospital.

1. Scott, R. W.; Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion: Clinical, Am. Heart J. **5**:68 (Oct.) 1929.

2. Porte, D., and Pardee, H. E. B.: The Occurrence of Coronary T-Wave in Rheumatic Pericarditis, Am. Heart J. **4**:584 (June) 1929.

differences in the electrocardiogram in the two conditions. To this end a careful comparative analysis of the serial electrocardiograms in our own series of cases together with those found in the literature has been undertaken.

REVIEW OF THE LITERATURE

The literature on the electrocardiographic findings in cases of pericarditis has accumulated in the last decade. In 1923 Oppenheimer and Mann [3] reported as significant findings a striking decrease in the voltage of the electrocardiograms of seven patients with pericardial effusion. No electrocardiograms were published. Scherf [4] later pointed out similar observations in 1926, but he did not publish his curves until 1930. Cohn and Swift,[5] in 1924, reported the occurrence of changes in the T wave in patients with rheumatic fever which they considered evidence of myocardial involvement. Further study of their three plates revealed that the patient whose electrocardiograms made up plate I had had precordial pain, while the patient whose electrocardiograms were shown in plate II had had a definite pericardial friction rub; unfortunately, there was no clinical history to go with plate III. In the first case slight changes occurred in the RS-T sector and T wave in leads II and III. A small inconspicuous Q wave was present in those leads, which, however, showed no change in size or configuration throughout the illness. In the second instance, definite deviations in the RS-T sector with a paradoxical relationship in leads I and III were apparent, and these were followed eighteen days later by negativity of the T wave in lead I. The significance of these observations is minimized owing to the fact that digitalis had been administered. There were no Q waves.

Gager,[6] in 1924, reported a case of pericardial effusion of uncertain etiology in a patient with organic heart disease and emphasized the disturbance in auriculoventricular conduction time. In addition, the electrocardiogram showed a decrease in voltage, changes in the RS-T segment with a paradoxical relationship in leads I and III, and abnormalities of the Q wave as well as of the T wave. An additional curve taken immediately following the removal of 500 cc. of exudate showed disappearance of the auriculoventricular block and the alterations of the RS-T segment and an increase in voltage. Subsequent curves taken

3. Oppenheimer, B. S., and Mann, Hubert: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. & Med. **20**:431, 1923.

4. Scherf, D.: Ein elektrokardiographisches Zeichen bei Erguss im Herzbeutel, Wien. klin. Wchnschr. **43**:298 (March 6) 1930; Wien. med. Wchnschr. **7**: 226, 1927.

5. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1 (Jan.) 1924.

6. Gager, L. T.: Conduction Changes Accompanying Pericardial Effusion with a Consideration of a Local Circulatory Factor in Heart Block, Arch. Int. Med. **33**:449 (April) 1924.

eighteen and twenty-two months after the onset revealed a progression of the inversion of the T wave and a gradual increase in the depth of the Q waves which were originally present.

In the series of patients with uremia and severe chronic nephritis studied by Wood and White,[7] the cases of two with a complicating pericarditis were presented with their electrocardiograms. In one instance (case 2) pericardial effusion was the terminal event, and an electrocardiogram taken four days before death revealed a marked positive deviation of the RS-T segment from the iso-electric level in leads I and II and slight deviation in lead III. The authors concluded that the toxic effect of uremia on the cardiac muscle was the most likely explanation of the rapidly changing electrocardiographic complexes. In the other case (case 3), acute pericarditis was noted at autopsy. The electrocardiogram taken the day before death showed slight elevation of the RS-T segment above the iso-electric level in lead I, and all the T waves were increased in amplitude, with sharpened apexes similar to those which we have encountered in the electrocardiograms of goats with experimental pericarditis.[8] There were no significant changes in the Q wave in either case.

Porte and Pardee,[2] in a study of three cases of acute rheumatic pericarditis, called attention to the finding of "coronary T waves" in the presence of this disease. They did not consider the possibility that the pericardial involvement accounted for the electrocardiographic changes and attributed them to a complicating myocardial inflammatory reaction. In all instances there were negativity of the T waves and upwardly convex RS-T sectors in the significant leads. There were no Q waves apparent in any of the cases. In their third case, a curve taken two months after recovery revealed a disappearance of the abnormalities of the T wave previously present.

Scott, Feil and Katz [1] reported changes in the RS-T segment of the ventricular complexes in three cases of pericardial involvement. In the first case, one of hemopericardium resulting from a ruptured aneurysm, there was a striking positive deviation of the RS-T sector in all three leads. Thirty-three days later the abnormalities of the RS-T sector had practically disappeared and T_1 was diphasic, with inverted T_2 and T_3. The latter changes were not commented on. At autopsy both the visceral and the parietal layer of the pericardium

7. Wood, J. E., Jr., and White, P. D.: The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, Am. J. M. Sc. **169**:76 (Jan.) 1925.

8. Herrmann, G. R., and Schwab, E. H.: Some Experimental and Clinical Electrocardiographic Observations on RS-T and T Changes in Pericarditis, Tr. A. Am. Phys. **49**:229, 1934. Herrmann, G. R.; Williams, H., and Williams, D.: Proc. Soc. Exper. Biol. & Med. **31**:1050, 1934.

were greatly thickened and were covered by a partially organized blood clot. The second case was one of suppuration in the pericardial sac, and the curves displayed similar but not as prominent abnormalities of the RS-T segment, with a small Q_2 and a more pronounced Q_3. The last case was one in which rheumatic pericardial effusion was suspected, but not proved. There was a positive elevation of the RS-T sector in all three leads, which disappeared nineteen days later. At that time a flattened T wave was present in all leads. In the initial curve an inconspicuous Q wave in leads I and II was noted, which was not present in the final electrocardiogram. These observers attributed the abnormalities of the RS-T segment to an anoxemic state of the cardiac muscle resulting from the increased hydrostatic pressure within the pericardial sac.

The electrocardiograms in Scherf's [4] case showed low voltage of the complexes in all leads. Following aspiration, an increase in amplitude of the waves occurred and, in addition, negativity of the T wave in leads II and III; the latter finding disappeared some time later. There were no Q waves.

Agostoni and Papp [9] recorded two cases of rheumatic pericardial effusion with electrocardiographic studies. Both cases were unusual in that they showed auriculoventricular as well as bundle branch conduction disturbances, the latter finding invalidating to a certain extent the T wave changes present. Rather prominent Q waves were present in the first case and persisted. In the second instance a Q wave was present in lead III.

In the electrocardiograms in the case of pyopericardium studied by Harvey and Scott,[10] there was a high take-off of the RS-T segment in all leads, but it was more pronounced in leads I and II. Following repeated aspiration and finally surgical drainage, the changes nearly disappeared. There was a gradual and pronounced decrease in the voltage of the T wave. An inconspicuous Q wave persisted in leads II and III.

An additional case of purulent pericarditis with electrocardiographic study was reported by Purks.[11] The single electrocardiogram revealed a marked positive deviation of the RS-T sector in all leads with slight negativity of the T wave in leads I and II and an iso-electric T_3. There

9. Agostoni, G., and Papp, C.: Gibt es elektrokardiographische Zeichen bei Herzbeutelerguss? Wien. klin. Wchnschr. **43**:842 (July 3) 1927.

10. Harvey, J., and Scott, J. W.: Changes in the Electrocardiogram in Course of Pericardial Effusion with Paracentesis and Pericardiotomy, Am. Heart J. **7**:532 (April) 1932.

11. Purks, W. K.: The Occurrence of a Coronary T-Wave in Purulent Pericarditis, South. M. J. **24**:1032 (Dec.) 1931.

were no Q waves. At necropsy the pericardial sac contained about a liter of pus, and the myocardium subjacent to the visceral pericardium showed an inflammatory reaction.

REPORT OF CASES

The case histories and serial electrocardiographic studies of seven cases of pericardial disease are presented. In six cases fluid of some type was present in the pericardial sac. The etiologic factor was rheumatic fever in two instances, tuberculosis in one and streptococcic suppuration in one; there was one case of polyorrhomenitis or Pick's disease and one of hemopericardium following a gunshot wound. There was one case of acute fibrinous pericarditis without effusion of streptococcic origin. The majority of the cases were in young persons, and in each instance the presence of organic heart disease and recognizable pathologic processes of the coronary arteries could be definitely excluded.

CASE 1.—*History.*—W. R., a Negro, aged 48, was first seen in the outpatient department of the John Sealy Hospital on Feb. 26, 1932, with the complaint of a sore throat. Examination revealed an acutely inflamed pharynx. The temperature was 101 F. The condition was treated locally, and the patient was advised to return the following day. He was not seen again until February 29, when he stated that his condition had become progressively worse. The fever had increased, and pain had developed in the left side of the chest. A slight cough with scanty expectoration had appeared. It was felt that hospitalization was necessary.

The past history was inconsequential. The patient said that he had never had a venereal infection. The family history revealed that his parents were both living, aged 85 and 80, respectively.

Examination.—Physical examination showed a man who appeared older than the stated age of 48 years and who was acutely ill. His temperature was 103 F.; the pulse rate was 124, and the respirations numbered 26 per minute. The throat was acutely inflamed and edematous, and at the base of the uvula there was a necrotic ulcer. The cervical glands at the angle of the jaws were enlarged and tender. Diminished expansion over the base of the left lung was apparent, and posteriorly crepitant and subcrepitant râles were heard. The area of cardiac dulness was found to be slightly increased by percussion. The heart sounds were well heard, and no murmurs or other adventitious sounds were present. The blood pressure was 130 mm. of mercury systolic and 95 diastolic. The pulse rate was rapid and regular. The radial arteries were moderately thickened. Abdominal examination revealed no areas of tenderness, and the liver and spleen were not palpable.

Examination of the urine gave negative results except for a few hyaline casts. The hemoglobin content was 75 per cent; the red blood cells numbered 3,460,000 per cubic millimeter, and the white blood cells, 3,350, with essentially a normal differential count. The complement-fixation test for syphilis was negative. A smear from the throat was negative for diphtheria but showed many short chain streptococci.

Progress.—The patient failed to improve under treatment. Dyspnea and precordial pain became prominent symptoms. On March 4, a pericardial effusion was suspected and confirmed by roentgenographic study. On this date auricular

fibrillation with a rapid ventricular rate appeared. On March 5, material was aspirated from the pericardium, and a thick, purulent exudate was obtained, which on culture yielded a rich growth of short chain streptococci. The leukocytes rose to 15,000 per cubic millimeter, with 86 per cent granular forms. A Schilling count revealed a 25 per cent shift to the left. Large doses of digitalis failed to control the auricular fibrillation. The pericardium was again aspirated on March 8, a similar exudate being obtained. The patient's condition rapidly became worse, and death occurred on March 9.

Necropsy.—From the pericardium was obtained about 800 cc. of a greenish-gray purulent material containing large amounts of fibrin. The heart was covered with a shaggy coat of this material and weighed 300 Gm. No significant valvular lesions were noted. The coronary arteries were remarkably free from sclerotic

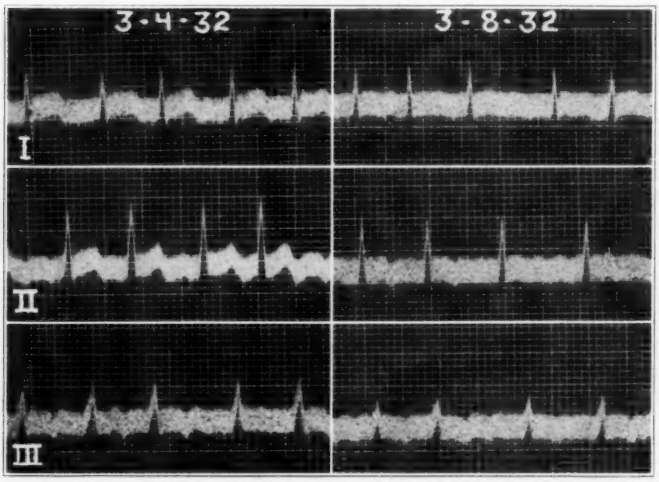

Fig. 1 (case 1).—Electrocardiograms in a fatal case of acute purulent streptococcic pericarditis following a streptococcic sore throat. The gradual accumulation of fluid in the pericardial sac was evidenced by serial teleoroentgenograms which showed 22 per cent enlargement on March 4, 25 per cent on March 5 and 32 per cent on March 7. Descriptions of these and subsequent electrocardiograms are found in the text.

changes. Marked hypostatic pneumonia was present. The liver, spleen and kidneys showed considerable cloudy swelling.

Acute purulent streptococcic pericarditis was the evident diagnosis.

Electrocardiograms.—Unfortunately only two electrocardiograms were taken, both after the advent of auricular fibrillation (fig. 1). The first, taken on March 4, before the administration of digitalis, showed a slight elevation of the RS-T sector in leads I and II; T_3 was sharply inverted. Rather marked slurring of the QRS complex was present in all leads. Four days later the RS-T segments had returned to the iso-electric levels. T_1 was flattened, and T_2 and T_3 had become sharply inverted and were preceded by an upward convexity of the ST interval.

There were no Q waves. In view of the administration of digitalis in this case, the significance of the changes in the T wave is open to question. It may be said, however, that they do not conform to the type generally found following digitalization.

CASE 2.—*History.*—A. D., a senior medical student, aged 26, was admitted to the John Sealy Hospital on March 21, 1932, with the complaint of general malaise, weakness and fever. One week before admission he had acute nasopharyngitis associated with a severe sore throat. The latter condition was treated locally, and all symptoms disappeared in about three days. Two days later he began to feel weak and dizzy, lost his appetite and felt as if he had fever. On the day of admission, while sitting in class, he chanced to place his hand over the precordium and immediately recognized the presence of a pericardial friction rub. There had been no pain.

The patient's past history did not reveal tonsillitis or any manifestation of rheumatic fever or chorea. At the age of 10 years he had suffered an attack of influenza, which was mild. There was no history of any venereal disease. The family history was irrelevant.

Examination.—Physical examination revealed a well nourished young man who did not appear acutely ill. His temperature was 100.4 F.; the pulse rate was 96, and the respiratory rate was 20. The tonsils were small, but along with the pharynx showed a mild hyperemia. The cervical glands were not enlarged. On palpation over the precordium a definite friction fremitus was noted. The heart was normal in size on percussion. On auscultation a loud, harsh, grating friction rub was heard. There were no murmurs. The blood pressure was 135 mm. of mercury systolic and 85 diastolic. Examination of the chest gave entirely negative results. No tenderness was present in the abdomen, and the liver and spleen were not palpable.

Laboratory examinations showed a hemoglobin content of 82 per cent, a red blood cell count of 3,880,000 and leukocytosis, the white blood cell count being 15,150 with 73 per cent polymorphonuclear forms. The urine was normal.

A teleoroentgenogram revealed a heart of normal size and configuration.

A diagnosis of acute fibrinous pericarditis of probable rheumatic streptococcic origin seemed justifiable.

Progress.—A low grade fever with the peaks of temperature reaching 100 F. persisted for eight days. The friction rub gradually became less intense and disappeared at about the same time that the temperature returned to normal. Repeated roentgenographic studies failed to demonstrate, at any time, any evidences of increased fluid in the pericardial sac. A sinus tachycardia persisted for several weeks.

The patient was discharged on May 29, apparently completely recovered. He has returned at intervals for follow-up studies, and at no time have any evidences of heart disease been found.

Electrocardiograms.—The electrocardiograms are shown in figure 2. The initial curve, on March 21, revealed low voltage of the QRS complex in all leads, with marked slurring. T_1 and T_2 were upright but of low voltage, and T_3 was iso-electric. One week later, on March 28, T_1 had become sharply inverted and was preceded by an upward convexity of the RS-T segment. Associated with this change there was an increase in the voltage of T_3. On April 6, T_2 had assumed a configuration similar to that in lead I. On April 20, T_1 and T_2 had again become upright but were of low voltage. On subsequent curves the voltage

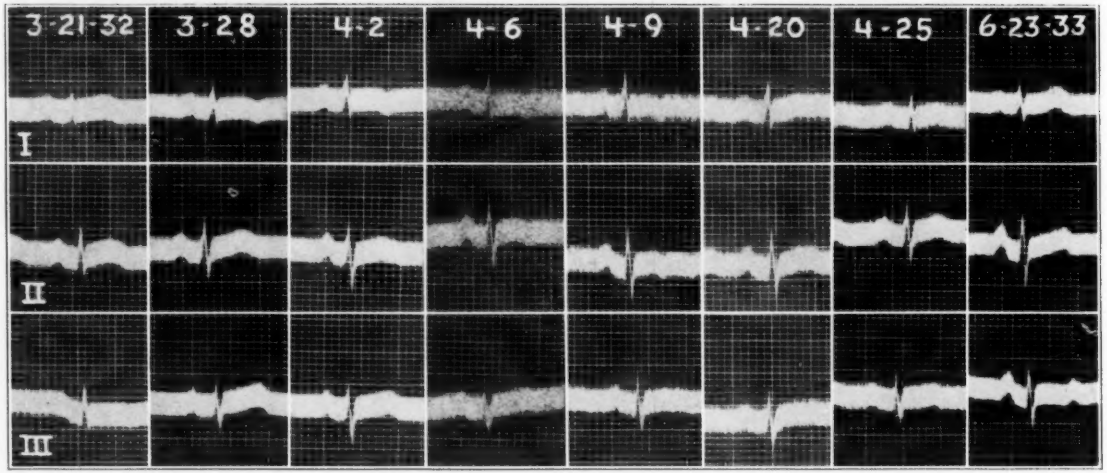

Fig. 2 (case 2).—Electrocardiograms in a case of acute fibrinous pericarditis without effusion of probable rheumatic origin with complete recovery.

of the T waves increased. Throughout the course of the illness there was no definite change in the voltage and configuration of the QRS complex. The last curve, taken on June 23, 1933, did, however, show a slight increase in voltage of the ventricular complex. At no time was there any deviation of the RS-T segment from the iso-electric level. No Q waves appeared.

CASE 3.—*History.*—D. S., a white man, aged 22, was admitted to the John Sealy Hospital on Jan. 11, 1932, because of shortness of breath and pain in the chest. He had not been in good health for several months because of repeated respiratory infections. He first noticed pain in the lower portion of the left side of the chest two weeks prior to admission. This pain was evanescent, but gradually increased in intensity. Fever was noticed at times, but it was not thought to be high. On January 8, the patient had a severe chill followed by high fever. That night he became very short of breath and spent the greater part of the night in the sitting position. The pain increased in intensity. A severe cough developed with the expectoration of blood-streaked sputum. He had had little appetite and had lost between 5 and 10 pounds (2.3 and 4.5 Kg.) in weight during the past few weeks.

In childhood he had had measles, mumps and chickenpox. Pneumonia in 1926 was followed by an attack of acute rheumatic fever which lasted for five weeks. In September 1931, he had a penile chancre, which had not completely healed when he came to the hospital. The family history was inconsequential.

Examination.—Physical examination showed an acutely ill young man who was in considerable respiratory distress. His temperature was 102 F.; the pulse rate was 110, and the respiratory rate was 20 per minute. Slight cyanosis of the forehead, lips and cheeks was present. There was no maculopapular rash on the skin. No mucous patches could be found in the mouth. The tonsils were small and embedded. A moderate amount of pyorrhea alveolaris was present. The chest was of normal size. The respiratory excursion was decreased over the posterior aspect of the left side of the chest below the angle of the scapula, and there were increased tactile fremitus, dulness on percussion, bronchial breathing and bronchophony. No râles were heard.

There was slight prominence of the precordium. The apex impulse was neither visible nor palpable. The area of cardiac dulness was increased both to the right and to the left. On auscultation over the precordium a loud, leathery pericardial friction rub was heard. The pulse was easily compressible and regular, had a rate of 108 per minute and was not paradoxical. The blood pressure was 110 mm. of mercury systolic and 78 diastolic. Considerable tenderness was encountered in attempted palpation of the upper part of the abdomen. The liver and spleen were not palpable. None of the joints of the body showed evidence of disease. On the undersurface of the glans penis, a raised, ulcerated area was present, which appeared to be healing. There was no edema of the extremities.

Examination of the urine gave negative results. The hemoglobin content was 64 per cent; the red blood cells numbered 3,610,000 per cubic millimeter, and the white blood cells, 13,200, with 66 per cent polymorphonuclear forms. The complement-fixation and precipitation tests for syphilis were strongly positive. The blood culture was negative. A teleoroentgenogram taken on admission revealed evidence of a moderate degree of pericardial effusion.

Progress.—With complete rest in bed and the administration of salicylates, the patient's condition gradually improved. The friction rub progressively became less intense and disappeared on the eighth day along with the fever. A teleoroentgenogram taken on January 22 showed a considerable decrease in the size of

the cardiac shadow, and on January 29 the fluid had apparently been entirely reabsorbed and the heart was reported to be normal in size and configuration. Recovery from the pericarditis was rapid and complete, and the patient was discharged on February 10. Cardiovascular examination at that time revealed no abnormalities.

Acute syphilitic pericarditis is a rare condition, and the previous history, together with the high fever, leukocytosis and response to salicylates, seems to establish the diagnosis of acute rheumatic pericarditis with effusion.

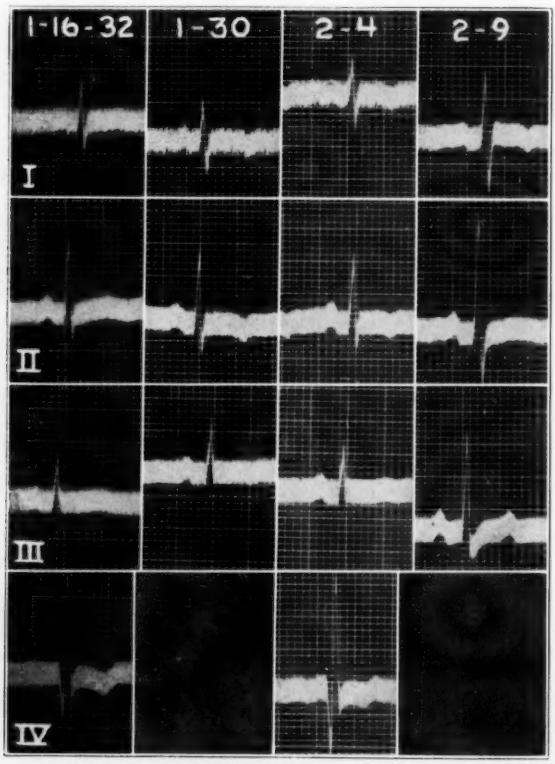

Fig. 3 (case 3).—Electrocardiograms in a case of acute rheumatic serofibrinous pericarditis. Teleoroentgenograms taken on January 12 revealed 32 per cent enlargement of the cardiac shadow; on January 22, 20 per cent enlargement, and on January 29, a cardiac silhouette of normal size and configuration.

Electrocardiograms.—The electrocardiograms are shown in figure 3. In this case, although an effusion was definitely present, no abnormalities of the RS-T segment were noted. The initial electrocardiogram, taken on January 16, was essentially normal except for the low voltage of the T wave in all leads. Lead IV, however, was considered as being abnormal. Two weeks later, January 30, inversion of the T wave was present in all leads, particularly in derivations I and

II, along with an upward convexity of the RS-T sector. Five days later, on February 4, this change was still present with the exception that T_3 had become positive. The last curve, taken on February 9, revealed an upright T_2 and T_3, T_1 still being definitely inverted. Electrocardiograms taken in three positions at that time revealed some fixation of the electrical axis, but it was not complete. Unfortunately, the patient could not be followed and no further electrocardiographic studies were made. There were no Q waves.

CASE 4.—*History.*—W. D., a white fisherman, aged 32, entered the John Sealy Hospital on Jan. 12, 1932, because of pain in the chest and shortness of breath. He dated his illness from Dec. 4, 1931, when he first noticed an aching pain beneath the upper portion of the sternum which radiated upward to the left shoulder and posteriorly to the left scapula. This pain was made worse by stooping, changing position, coughing or deep breathing. At the same time the patient began to notice some shortness of breath. This seemed to disturb him most when he was lying down, especially at night after going to bed. To get relief he would have to sit up in bed. These symptoms persisted for three days and then disappeared.

About December 24, while tonging oysters, he again became short of breath. The pain in the chest reappeared soon thereafter. This attack, of the same character, came on and gradually increased in severity, finally causing him to come to the hospital. A troublesome dry, hacking cough was present. Fever had been present for several days. A roentgenogram of the chest taken on January 9 revealed no abnormality.

Each winter for many years the patient had had many respiratory infections. In 1927 he was operated on for an abscess of the abdominal wall. In 1910 he had a penile chancre, followed by a cutaneous eruption, for which he received a negligible amount of therapy. During childhood he had had mumps, whooping cough and bloody diarrhea, the last-mentioned condition recurring at irregular intervals ever since. The family history was inconsequential.

Examination.—Physical examination showed a white man of about the stated age of 32, who appeared to be in considerable pain and respiratory distress. The cervical veins were abnormally distended. The mouth and pharynx were in a poor hygienic state. Examination of the chest gave negative results except for the physical signs indicating compression of the base of the left lung posteriorly. Palpation of the precordium revealed a faint friction fremitus. On percussion the area of cardiac dulness was increased both to the right and to the left, and the configuration was definitely altered by changes in position. On auscultation a loud to-and-fro friction rub was heard over the third and fourth left intercostal spaces, synchronous with heart action. The heart sounds were of fair quality but distant. The pulse rate was 100; the rhythm was regular. The blood pressure was 116 mm. of mercury systolic and 74 diastolic. The peripheral arteries showed no sclerosis. The edge of the liver was felt just below the costal margin. The spleen was not palpable. An indolent ulcer was present on the anterior aspect of the left leg.

Examination of the urine gave negative results. The hemoglobin content was 76 per cent; the red blood cell count was 4,250,000 per cubic millimeter, and the white blood cells numbered 10,400, with 55 per cent polymorphonuclear forms. Complement-fixation and precipitation tests for syphilis were negative. Examination of the stool failed to reveal Endamoeba histolytica. A teleoroentgenogram taken on January 12 revealed the presence of a pericardial effusion.

Progress.—Intermittent fever was present for eight days, the peaks of temperature being around 103 F., with a corresponding increase in the pulse and respira-

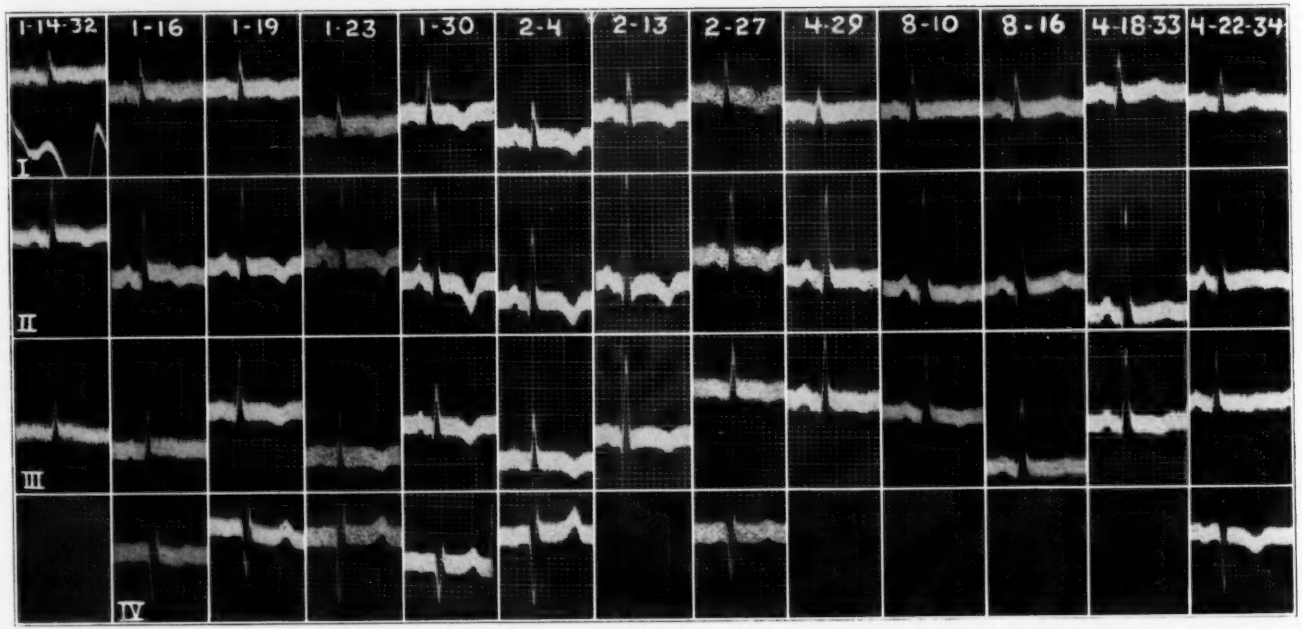

Fig. 4 (case 4).—Electrocardiograms in a case of acute and subacute serofibrinous pericarditis of rheumatic origin. Teleoroentgenograms taken on January 12 revealed 33 per cent enlargement of the cardiac shadow; on January 13, 49 per cent enlargement, and on January 22, 5 per cent.

tory rates. On the fifth day of salicylate therapy the symptoms began to subside. A teleoroentgenogram taken on January 22 showed that the pericardial effusion had been reabsorbed and that the size and configuration of the heart were normal. Recovery was uninterrupted, and the patient was discharged on March 1. He has been seen on several occasions since that time and has had no recurrence of symptoms or signs.

The diagnosis of acute rheumatic pericarditis with effusion seemed to be warranted.

Electrocardiograms.—The numerous electrocardiographic studies made and the date on which each was taken are depicted in figure 4. In the first two electrocardiograms, taken on January 14 and 16, there was a definite elevation of the RS-T segment above the iso-electric level in the three conventional leads, terminating in a negative T wave. Lead IV on January 16 similarly showed deviation of the RS-T sector. With the disappearance of the accumulation of fluid in the pericardial sac there was a return of the RS-T segment to the base line, and coincidentally, the degree of negativity of the T wave became more marked and the voltage of the QRS complex increased. Coincident with the inversion of the T wave in the usual leads, there was an increasing degree of positivity in the anteroposterior chest lead. On February 13 the inverted T wave was preceded by a well defined upward convexity of the RS-T interval in all leads. Three and one-half months after the onset of the illness T_1 had become positive but was low in voltage. Subsequently, on August 16, T_1 had increased in voltage and T_2 had become upright, although T_3 remained inverted. Curves taken approximately eight, sixteen and twenty-four months later showed that the condition had become stationary as no further significant changes were observed. Electrocardiograms taken in three positions on Feb. 13 and Aug. 16, 1932, and April 22, 1934, showed no fixation of the electrical axis. In the initial electrocardiograms a Q wave was present in leads I and II, and later this wave appeared in lead III. Its depth and configuration were similar to those encountered in many normal curves, and, furthermore, no significant changes in this component of the ventricular complex occurred throughout the period of study.

Case 5.—*History.*—G. W., a Negro laborer, aged 33, was admitted to the John Sealy Hospital on Feb. 24, 1933, because of shortness of breath and weakness. Seven weeks before entry he began to have night sweats. About a week later he noticed that he became short of breath after mild exertion and that his heart would beat very fast. He suffered no actual pain, but at times he had a sense of oppression in the left side of the chest. He thought that he had had fever every night since the sweats began, but he had not used a thermometer. On arising in the morning he usually coughed some, expectorating a mucopurulent sputum. He had never coughed up or expectorated blood. There had been a loss of weight of 6 pounds (2.7 Kg.), although the appetite had remained good.

In June 1932, he had an attack of acute appendicitis. Operation was advised, but he refused and the condition subsided. During 1927 he was under treatment several weeks in the outpatient department for a right pleural effusion, which was apparently reabsorbed. During the winter of 1926 he was hospitalized a few days because of a severe attack of bronchitis. In the same year he contracted gonorrhea, for which he was treated six months. At this time there was present also a penile sore which was cauterized. During childhood he had measles, whooping cough, mumps and "chills and fever." The family history was irrelevant.

Examination.—Physical examination revealed a well nourished Negro of about the stated age of 33, who did not appear acutely ill. His temperature was 99 F.;

his pulse rate was 90 per minute and his respiratory rate 20. The pupils were equal and reacted to light and in accommodation. The sclerae showed no icterus. The tonsils were small and innocent in appearance. There were no palpable cervical glands. The chest was of the sthenic type. Slight dulness on percussion was present in the base of the left lung. There were no changes in the breath or the voice sounds, and no adventitious sounds were heard.

Palpation of the precordium gave negative results. On percussion the area of cardiac dulness was considerably enlarged in all directions. A definite change in the size of the area of retromanubrial dulness was noted when the patient assumed the upright position. On auscultation a definite pericardial friction rub was heard in the third and fourth interspaces to the left of the sternum. The heart sounds were of fair quality and intensity. The aortic second sound was

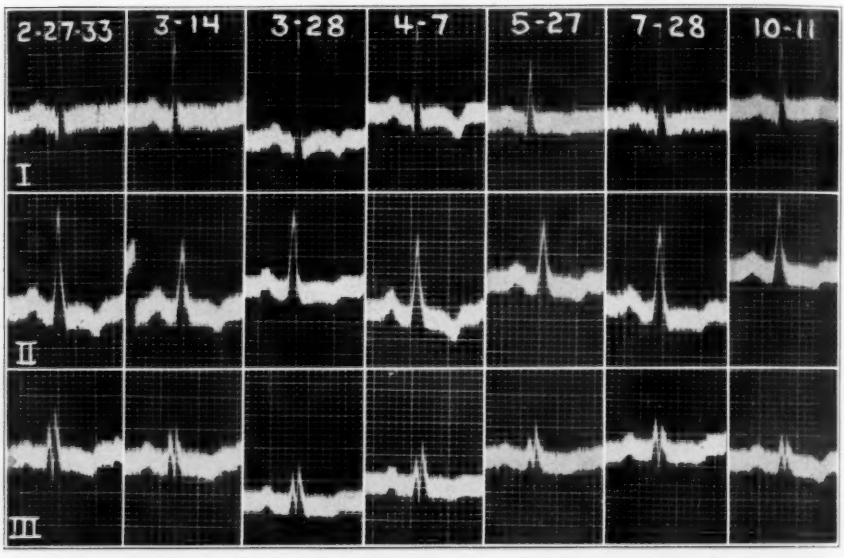

Fig. 5 (case 5).—Electrocardiograms in a case of subacute to chronic serofibrinous pericarditis of tuberculous origin. The degree of enlargement of the cardiac shadow shown by the roentgenogram was 22 per cent on February 25, 26 per cent on March 18 and 15 per cent on April 17.

moderately accentuated. No murmurs were heard. The pulse rate was 90 per minute, and the rhythm was regular. The blood pressure was 124 mm. of mercury systolic and 90 diastolic in both arms. The liver was just palpable below the costal margin but was not tender. The spleen could not be felt. There was no edema of the extremities.

Examination of the urine revealed a trace of albumin. The hemoglobin content was 80 per cent; the red blood cells numbered 4,680,000 per cubic millimeter, and the white blood cells, 4,200, with an essentially normal differential count. The complement-fixation and precipitation tests for syphilis were negative.

A teleoroentgenogram taken on admission showed a marked increase in the cardiac measurements, although the configuration was not typical of that of a pericardial effusion. A diagnostic paracentesis was not done, but in view of the fact that subsequent roentgenographic studies revealed a considerable decrease in the size of the shadow, it seems logical to conclude that a pericardial effusion had been present.

Progress.—Low grade fever was present for the first week, the temperature never exceeding 100 F. The pulse rate remained elevated after the temperature returned to normal. On the sixth day the pericardial friction rub disappeared. A teleoroentgenogram taken on March 18 showed a decrease in the cardiac measurements, and another taken on April 17 revealed a further reduction in size and a heart shadow which was essentially normal in outline. The patient's condition improved rapidly. He gained 17 pounds (7.7 Kg.) in weight and was discharged from the hospital on April 28. He has been seen on several occasions since that time and has remained well.

The diagnosis of acute tuberculous pericarditis with effusion seems to be justifiable.

Electrocardiograms.—The electrocardiogram taken on admission (fig. 5) revealed a T wave of low voltage in lead I with sharp inversion in leads II and III. In leads II and III a slight upward convexity of the RS-T segment was present, but otherwise there was no deviation from the iso-electric level. The significant changes in subsequent electrocardiograms occurred in lead I, little change taking place in leads II and III. On March 14, the first evidence of negativity of T_1 appeared. Two weeks later the final deflection in lead I was sharply inverted and preceded by a marked convexity of the RS-T interval, originating on the iso-electric line. This degree of negativity of T_1 increased for a time and then gradually became less, and the curve taken on July 28 revealed a flat T_1. In the electrocardiogram taken on November 11, T_1 had become positive but was of low voltage. Electrocardiograms taken in three positions on March 1, 1934, revealed practically complete fixation of the electrical axis. No significant Q waves appeared.

CASE 6.—*History.*—L. C., a Negro laborer, aged 24, was first admitted to the John Sealy Hospital on April 11, 1932, because of pain in the chest. He dated his illness from March 30, 1932, on which day he had had a severe chill followed by high fever and a profuse sweat. Three days later a dull aching substernal pain developed, which gradually became worse. This pain seemed to him to be deep in the chest, and it was made definitely worse by deep breathing. He had no more chills after the initial one but continued to have fever. Four days before the onset of his illness he had had a cold in the head, but he had had no cough at any time. There had been a loss of 20 pounds (9.1 Kg.) in weight within a month, but he attributed this to hard work. There were no urinary symptoms.

At the age of 19 he had had a bout of fever which lasted for three weeks. He stated that his physician at this time had been unable to determine the cause of the fever. He had contracted gonorrhea at the age of 14, which he stated had been cured. He said that he had never had a primary lesion. Except for an attack of fever which had been diagnosed as malaria, no childhood diseases were recalled. The family history was inconsequential.

Examination.—Physical examination revealed a well nourished Negro of about the stated age of 24, who did not appear acutely ill. His tempertaure was 100.8 F.; the pulse rate was 96, and the respirations numbered 26 per minute. The tonsils were hypertrophied and appeared moderately inflamed. A few shotty cervical

glands were palpable. The lungs were normal except for the presence of a few coarse moist râles in the base of the right lung, posteriorly. These râles disappeared within a few days. The heart was normal in size and shape, and no murmurs were heard. The blood pressure was 140 mm. of mercury systolic and 90 diastolic. The peripheral arteries were soft. The liver and spleen were not palpable.

The urine examined on several occasions always contained pus cells but showed no other abnormalities. The hemoglobin content was 75 per cent; the red blood cells numbered 4,210,000 per cubic millimeter, and the white blood cells, 7,750, with a normal differential count. The complement-fixation and precipitation tests for syphilis were negative. The Widal reaction was positive for Bacillus typhosus. The blood and stool cultures for typhoid bacilli were negative.

Roentgenographic study of the chest showed the presence of considerable inflammatory thickening in both lungs without, however, acceptable evidence of tuberculosis.

The remittent type of fever, the temperature never rising above 102 F., gradually became less and disappeared as the body temperature returned to normal on the twelfth day. The symptoms likewise disappeared, and the patient was discharged on April 25 apparently completely recovered. A satisfactory diagnosis was not made, the tentative opinion being that the patient had had mild typhoid fever.

He was readmitted to the hospital on May 11, with distressing shortness of breath and water-logging. He had felt well until May 10, when a severe pain had developed over the upper part of the abdomen, which lasted for only about three days. With the subsidence of the pain, swelling of the abdomen appeared. A few days later he noticed shortness of breath and swelling of the feet. The abdomen continued to increase in size. All symptoms progressively became worse, and for three nights before entering the hospital the patient was forced to sit up in order to breathe and consequently had slept very little.

Physical examination revealed an acutely ill patient. His temperature was 103 F.; his pulse rate was 118, and his respirations numbered 30 per minute. Definite cyanosis was present. The veins of the neck, as well as those of the upper extremities, were conspicuously engorged. Many moist râles were present in the bases of both lungs. The area of cardiac dulness was greatly increased both to the right and to the left of the sternum. The heart sounds were distant and indistinct. No murmurs or other adventitious sounds were heard. The pulse was paradoxical in type, at a rate of 118 per minute. The blood pressure was 150 mm. of mercury systolic and 90 diastolic. The venous blood pressure was 28 cm. of blood. A slight pitting edema over the shins was present. The abdomen was protuberant, and both shifting dulness and a distinct fluid wave were elicited. The liver and spleen could not be palpated owing to the accumulation of fluid.

Examination of the urine showed a trace of albumin, an occasional granular cast and a few leukocytes and erythrocytes. The blood study revealed red blood cells numbering 3,360,000, with a hemoglobin content of 60 per cent, and a white blood cell count of 8,900, with a normal differential count. The blood urea nitrogen was 23.4 mg. per hundred cubic centimeters. A blood culture was negative. The renal excretion of phenolsulphonphthalein dye amounted to 50 per cent in two hours. The Wassermann reaction of the blood was negative.

A teleoroentgenogram revealed the presence of a large pericardial effusion.

Progress.—Pericardial aspiration was done the second day after admission and yielded 300 cc. of a slightly blood-tinged fluid. Laboratory examination of this fluid revealed it to be definitely an exudate with a high lymphocyte count. The mechanical removal of the fluid resulted in some improvement. Increasing symp-

toms, however, made it necessary to repeat the pericardial puncture four days later, when removal of 700 cc. of a similar fluid relieved the urgent dyspnea. Abdominal paracentesis was attempted on May 19, but without success owing to the fact that the fluid coagulated spontaneously in the trocar. There was a gradual accumulation of fluid in the right side of the chest, which became so great in amount that a thoracentesis was done and 1.5 liters of fluid similar to that obtained from the pericardium was removed. Some time later fluid also appeared in the left pleural cavity.

The temperature remained high for about two weeks and then gradually became lower, returning to normal in about one month. There was no fever for the succeeding two months, and then rises in temperature occurred intermittently, the peaks, which usually occurred in the afternoon, reaching from 101 to 102 F. Inoculation of guinea-pigs with the fluid from both the pleural and the pericardial

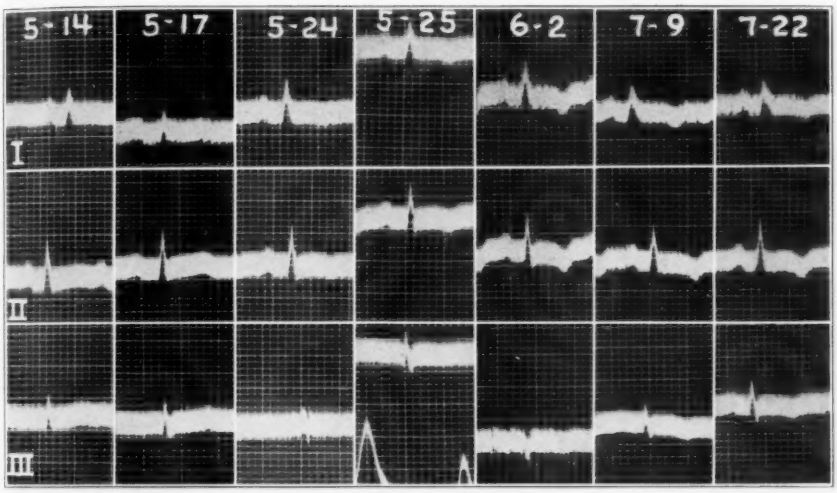

Fig. 6 (case 6).—Electrocardiograms in a case of subacute to chronic serous pericarditis, pleuritis and peritonitis. The pericardial effusion was great and persistent.

cavity did not yield any definite evidence as to the etiologic factor. Although inflammatory foci in the lungs, composed of epithelial and lymphocytic cells, suggested tuberculosis, this was not considered definite in view of the fact that no giant cells were found. Stereoscopic roentgenograms of the pulmonary fields demonstrated the absence of any lesion suggesting tuberculosis. In spite of the mechanical removal of the fluid and the dissipation of it by the use of mercurial and xanthine diuretics, the patient's condition was unimproved, and he gradually but progressively became worse. He became dissatisfied and left the hospital against our advice on September 17. Death occurred in a neighboring city approximately five months later.

The clinical diagnosis of multiple serositis or polyorrhomenitis was made.

Electrocardiograms.—Numerous electrocardiographic studies were made. Those depicting the significant changes that occurred are shown in figure 6. The out-

standing findings in the initial curve, taken on May 14, were a QRS complex of less than 5 millivolts in all three leads, associated with marked slurring, a flat T_1, and low voltage T_2 and T_3. There were no abnormalities of the RS-T segment. Ten days later, on May 24, early negativity of the T wave was observed in leads I and II, and subsequently, on May 25, T_3 became inverted. Further changes, registered June 2, consisted of an increase in the degree of negativity of the T wave and the appearance of an upward convexity of the RS-T interval. These retrogressed slightly but were still present on July 22. Little, if any, change occurred in the voltage of the ventricular complexes. No Q waves developed.

Electrocardiograms taken before and after paracentesis of the pericardium on two occasions, one before the appearance of the changes in the T wave and one after they had become marked, are shown in figure 7. It is to be noted that little,

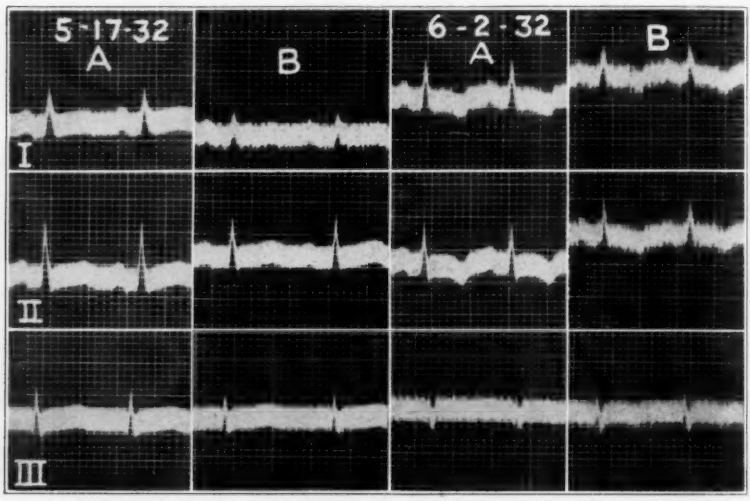

Fig. 7 (case 6).—Electrocardiograms taken before (*A*) and after (*B*) paracentesis of the pericardium during the early and late stages of the disease. Note the slight change in voltage and that the removal of fluid exerted no effect on the T waves.

if any, change in the T waves occurred. In the first instance 700 cc. of fluid was aspirated and in the second, 500 cc. In each instance there was a slight decrease in the voltage of the ventricular complexes after the removal of the fluid.

Case 7.—*History.*—E. W., a Negro laborer, aged 38, was admitted to the John Sealy Hospital at 2:30 a. m. on May 31, 1930. At 7:30 a. m. the previous day, in a nearby city, he had been shot with a shotgun from a considerable distance and had sustained numerous bird-shot wounds, two of which were in the anterior wall of the chest overlying the heart. He was seen by a physician at that time, who did not regard his injuries as being serious and who administered tetanus antitoxin. Shortly thereafter, however, shortness of breath and pain in the epigastrium and precordium appeared, all of which symptoms gradually increased in intensity.

Examination.—Physical examination revealed a Negro of about the stated age of 38, who appeared to be critically ill. Dyspnea was extreme, and definite cyanosis was present. The cervical veins were greatly distended. The pulse was very rapid and barely perceptible at the wrist. The blood pressure could not be recorded. A small puncture wound was present in the fourth left intercostal space about 2 cm. from the left sternal border, and another in the fifth left intercostal space about 4 cm. from the sternum. A marked increase in the area of cardiac dulness was noted on percussion. On auscultation, the heart sounds were feeble, indistinct and distant. Considerable tenderness was present in the upper part of the abdomen. The liver and spleen could not be felt.

A teleoroentgenogram revealed the presence of a large amount of fluid in the pericardium.

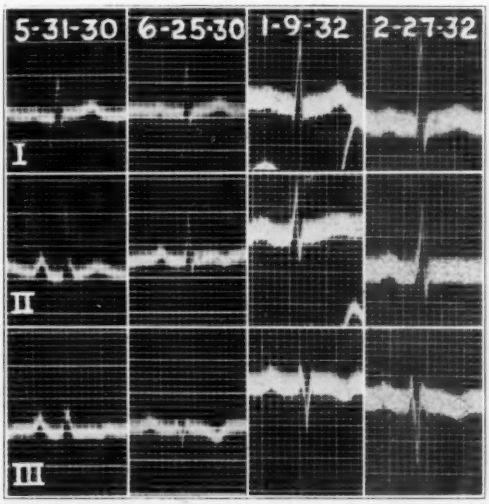

Fig. 8 (case 7).—Electrocardiograms in a case of hemopericardium following a gunshot wound. Severe heart tamponade was present and necessitated paracentesis. Recovery was complete.

In view of the urgency of the symptoms, paracentesis of the pericardium was done, and 250 cc. of blood was removed. The change in the patient's condition was dramatic. The blood pressure rose to 100 mm. of mercury systolic, the pain and dyspnea were much relieved and the patient appeared greatly improved. Four days later, on June 4, a teleoroentgenogram showed that considerable fluid remained in the pericardium. Nevertheless, his condition remained good, and at the end of two weeks the patient seemed to have made a complete recovery. An additional roentgenographic study was made on June 23, and at that time the cardiac shadow was of normal size and configuration. Two bird-shots were noted on the film; one was embedded in the wall of the chest, and the other, by fluoroscopy, was found to be embedded in the wall of the right ventricle.

Electrocardiograms.—The initial electrocardiogram taken on May 3, 1930, before aspiration of the pericardium was rather noncommittal from a diagnostic standpoint

(fig. 8). A slight positive deviation of the RS-T sector was present in leads I and II: T_1 and T_2 were upright and of fair voltage and T_3 was inverted. The P wave in derivations II and III was sharply peaked and of good amplitude. The second electrocardiogram, recorded on June 25, showed definite inversion of the T wave with an upwardly convex RS-T sector in leads II and III. A shift in the electrical axis had occurred. In addition, there was a rather striking change in the configuration and amplitude of the P wave. Subsequent curves were taken on Jan. 9 and Feb. 27, 1932. The T wave in lead II had become upright but was of low voltage, and T_3 remained sharply inverted. There was a progression of the shift of the electrical axis. Curves taken in three positions on February 27 showed some fixation of the electrical axis. No Q waves were apparent.

COMMENT

Our clinical observations and experimental studies,[8] with those of others,[12] seem to furnish conclusive proof that pathologic states of the pericardium are capable of producing definite and striking alterations in the electrocardiogram. Broadly speaking, these changes may be of three types: a decrease in the voltage of the QRS complex; deviations of the RS-T sector from the iso-electric level, and the progressive changes in the T wave the development and interpretation of which we are emphasizing as our contribution to the subject. The deviations of the RS-T sector and the decreased voltage usually occur early and in the presence of rapidly accumulating effusion or blood in the pericardium. The changes in the T wave come later and may or may not have been preceded by deviations of the RS-T sector. The abnormalities of the RS-T sector are not present in all cases of pericardial effusion, even in those instances in which the accumulation of fluid is great. In case 6, the amount of fluid present was sufficient to produce *Herztamponade* with extreme venous congestion, a decrease in systemic blood pressure and diastolic heart failure; yet the RS-T segment remained at the iso-electric level. A moderate degree of effusion was present in cases 3 and 5, and no changes in the RS-T interval were recorded. Extensive pericardial effusion, likewise, may not be accompanied by significant decrease in the voltage of the QRS complex of the electrocardiogram. In case 6 the initial deflection of the ventricular complex was less than 5 millivolts in all three leads. It is interesting to note that in this case, on two occasions, an electrocardiogram taken immediately following paracentesis with the removal of 700 and 600 cc. of fluid, respectively, showed an actual and unexplained decrease in the amplitude of the QRS complex (fig. 7). In case 2, one of acute fibrinous pericarditis without effusion, the QRS complex was less than

12. Katz, L. N.; Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion; Experimental, Am. Heart J. **5**:77 (Oct.) 1929. Foulger, M., and Foulger, J. H.: The Blood Pressure and Electrocardiogram in Experimental Pericardial Effusion, Am. Heart J. **7**:744 (Aug.) 1932.

5 millivolts in all leads, and this finding persisted without change throughout the course of the disease and after complete recovery. The amount of fluid present, the nature of the fluid substance, the rapidity of accumulation, the distensibility of the pericardial sac and the presence or absence of coronary sclerosis are factors which appear to determine whether or not these electrocardiographic signs will appear.

In the cases of pericarditis associated with an effusion that have been studied adequately by serial electrocardiograms, the disappearance of the changes in the RS-T segment was followed by definite alterations in the T wave. Similarly, in the cases of fibrinous pericarditis without appreciable exudation into the pericardial sac, successive changes in the T wave which were not preceded by deviations in the RS-T sector have been recorded. The alterations in the T wave are essentially identical in the two types of cases and consist, as a rule, of an upward convexity of the RS-T interval, which is followed by a sharply peaked, inverted T wave. In occasional cases in the literature no convexity of the RS-T sector or negativity of the T wave was present; there were merely iso-electric intervals and flattened T waves. These abnormalities of the end-deflection of the ventricular complex appear early and by the end of the first week or ten days are quite definite. As the condition progresses, the negativity of the T wave frequently becomes more marked and successively becomes apparent in all three leads, the initial change being, as a rule, in lead I. Subsequently, with the passage of the acute stage, the changes in the T wave gradually disappear, usually in the same order as they developed. In those cases in which recovery is apparently complete, the T wave again becomes upright in the significant leads. A careful study of the electrocardiograms here presented indicates that the changes in the final deflections of the ventricular complex are similar in many, but not in all, respects to those encountered in the healing stages of cardiac infarction.

AN EVALUATION OF THE ELECTROCARDIOGRAPHIC DIFFERENTIATION BETWEEN PERICARDIAL DISEASE AND CARDIAC INFARCTION

Acute pericardial disease, particularly when associated with pain, may simulate closely the syndrome of coronary thrombosis with infarction, and in view of the fact that pericarditis is a frequent finding in the latter condition the difficulty in differential diagnosis is obvious. When there are added to these clinical similarities almost identical electrocardiographic abnormalities, the diagnostic problem becomes still further involved. The importance of an exact diagnosis from a therapeutic as well as from a prognostic standpoint is self-evident. In lieu of pathognomonic electrocardiographic findings, our analysis of all available data offers some highly suggestive electrocardiographic signs,

which only careful scrutiny of serially taken curves will reveal and which when found should materially aid in arriving at an accurate diagnosis.

With reference to the abnormalities of the RS-T segment, it is to be noted that in pericardial effusion the elevation may occur in all three leads, or in leads I and II, there being no cases reported in which the RS-T sectors of lead II and lead III alone were abnormal. Furthermore, as Scott, Katz and Feil [1] pointed out, these deviations in the RS-T interval are always positive. The paradoxical relationship between leads I and III is not present in uncomplicated pericarditis. Exceptions to the latter rule are the cases of pericardial effusion reported by Gager [6] and Cohn and Swift.[5] In the former instance, the patient's age, the presence of hypertension and peripheral and fundal sclerosis and the sudden onset strongly suggest that a coronary thrombosis inaugurated the breathlessness and effusion. The Q waves in the initial curve and the subsequent electrocardiographic studies further support this contention. In Cohn and Swift's case the findings are somewhat obviated due to the fact that digitalis had been administered. Some of our observations, especially in the experimental animal, suggest that after deviations of the RS-T segment the return to the iso-electric level occurs sooner in pericardial effusion than in cardiac infarction; especially is this so when the increased intrapericardial pressure is relieved.

In the matter of abnormalities of the T wave, from the standpoint of configuration no differentiating evidence is forthcoming. The so-called "coronary" type of T wave is commonly encountered in cases of pericardial involvement. Inversion of the T wave in leads I and II in cases of pericarditis is seen, as a rule, during some stages of the disease, and negativity of the T wave is frequently present in all three leads. In contrast to the changes in the RS-T sector in cases of pericarditis, a paradoxical relationship of the T waves in leads I and III may be present in the early stages produced by a negative T_1 and a positive T_3 and in the later stages by a persistence of negativity of the T wave in lead III with a return of T_1 to positivity.

A further important point in differential diagnosis from an electrocardiographic standpoint seems to be found in a study of the initial deflections of the ventricular complex. As Wilson and his co-workers [13] have so ably pointed out, the changes in the Q wave following closure of the coronary artery with infarction are quite distinctive and frequently diagnostic. These changes occur in a high percentage of cases and usually appear following the disappearance of the abnormalities of the

13. Wilson, F. N.; Macleod, A. Garrard; Barker, Paul S.; Johnston, Franklin D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex. Heart **16**:155 (June) 1933.

RS-T segment. They are associated with the alterations of the T wave and frequently persist after the disappearance of the latter changes. In an analysis of the reported cases of pericarditis studied electrocardiographically, including those of this series, conspicuously abnormal changes in the Q wave were not observed except in those of Gager [6] and Agostoni and Papp.[9] As previously mentioned, Gager's case appears to be one of definite coronary artery disease. The electrocardiograms of the case of Agostoni and Papp revealed both auriculoventricular and bundle branch conduction defects and hence cannot be considered in this connection. In case 4 of this series, it is to be noted that an inconspicuous Q wave was present in all three leads. However, the Q waves are similar in size and configuration to those encountered normally and, furthermore, throughout the two year period of study they showed no appreciable change. It seems logical, therefore, to consider the presence of definite abnormalities of the Q wave as evidence in favor of the diagnosis of myocardial infarction rather than that of an uncomplicated pericarditis.

An anteroposterior chest lead, lead IV, was taken according to the technic of Wolferth and Wood,[14] in two of the cases herein reported. A review of the reported cases of acute obstruction of the coronary artery studied with the use of this additional lead reveals that when changes in the RS-T interval are present in the conventional leads they are likewise present in lead IV, frequently being more marked, and, furthermore, that deviations in the RS-T interval may be present in lead IV without being apparent in the conventional leads. Although the number of cases of pericarditis studied with the fourth lead is far too small to justify any conclusions, the findings hitherto reported as pathognomonic of occlusion and disease of the coronary artery have been noted. In case 4, definite deviations in the RS-T segment (slightly more than 1 millivolt) were present in the three conventional leads along with a similar but less marked change in the chest lead. Subsequently, with the development of changes in the T wave in the usual leads, further significant changes in lead IV appeared, consisting of a negative, humped RS-T segment with a positive coronary T wave. In the second instance of pericardial effusion (case 3), also studied with the fourth lead, no changes in the RS-T interval were present in the conventional leads. It is interesting to note, however, that in lead IV, before the appearance of changes in the T wave in the conventional leads, a type of change had occurred which has been considered suggestive of coronary artery disease.

14. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30 (Jan.) 1932.

THEORETICAL CONSIDERATIONS AS TO THE MECHANISMS UNDERLYING THE PRODUCTION OF THE ELECTROCARDIOGRAPHIC CHANGES IN PERICARDITIS

Our interpretation of the results of our clinical and experimental studies and those of others seem to indicate the presence of two distinct types of electrocardiographic changes occurring in different stages of pericardial processes: The one appearing during the acute stage often consists of elevation of the RS-T sector and decreased voltage of the ventricular complex, and the other, occurring later, is comprised of progressive and retrogressive changes in the T wave.

The deviations in the RS-T sector are apparently the result of ischemia of the cardiac muscle, occurring as the intrapericardial pressure rises to the point of collapsing the auricles, thereby hindering venous return, lowering the systemic pressure and pulse pressure and thus interfering materially with the blood flow through the right and left coronary arteries. This total involvement of the coronary flow is probably what accounts for the positive deviation of the RS-T sector in all leads.

The decreased voltage of the QRS complex seen in cases of pericardial effusion has been attributed to the change in the conducting medium surrounding the heart with a consequent short-circuiting or damping of the action currents. In view of the fact that numerous cases fail to show this electrocardiographic sign, it becomes necessary to consider other possibilities. Myocardial edema, pulmonary engorgement, pleural effusion and subcutaneous edema are other factors which might be operative in the production of this electrocardiographic abnormality.

As the changes in the T wave occur in cases of acute fibrinous pericarditis without effusion and, further, in view of the fact that these abnormalities also appear after the effusion has become reabsorbed and, in our animals, during healing, it seems likely that they are associated with organization and repair of the process in the epicardium and subepicardial myocardium. These changes occur regardless of the etiologic factor at work in the pericardial process. In other words, whether the organization is of tissue of rheumatic, tuberculous, pyogenic or nonspecific etiology, or even when it is the organization of blood that is deposited on the epicardium, the changes in the T wave are qualitatively the same. The length of time for which the abnormalities of the T wave persist, however, varies somewhat with the etiologic factor. In the tuberculous type, with a tendency to recurrent flare-ups, they may continue indefinitely, while in rheumatic pericarditis they usually clear up within a few weeks after subsidence of the symptoms. Apparently, with each recurrence the changes are more likely to persist, and the length of time they remain apparent may be considered as

somewhat of an index to the degree and extent of involvement. In cases of hemopericardium, in which drainage is done by paracentesis and in which there is no recurrence, the T waves return to normal much sooner than in cases in which the blood is allowed to remain in the pericardium.

SUMMARY

Seven cases of pericardial disease of various types are presented with abstracts of the clinical histories, complete physical and pertinent laboratory data and serial electrocardiographic studies.

A complete review of the available literature on the subject has been attempted.

The similarity of the deviations in the RS-T sector in cases of pericardial effusion to those occurring in cases of coronary thrombosis with infarction is reiterated.

Attention is directed to the previously unmentioned but significant inversions of the T wave which follow the changes in the RS-T segment in cases of excess fluid in the pericardial sac following reabsorption, thus continuing the electrocardiographic analogy between pericardial effusion and cardiac infarction.

The occurrence of progressive changes in the T wave in acute fibrinous pericarditis without an accompanying effusion and without preceding abnormalities in the RS-T segment is emphasized.

An evaluation of the electrocardiographic differences between pericardial disease and cardiac infarction is presented. The absence of the development of significant abnormalities of the Q wave in pericardial pathologic processes is stressed. No information of differential diagnostic value is apparently to be derived from the use of lead IV.

Some theories as to the mechanisms operative in the production of the types of electrocardiographic changes encountered, based on our clinical and experimental studies, are brought forth. The changes in the RS-T sector are apparently the result of ischemia of the cardiac muscle, and the progressive and retrogressive changes in the T wave seem to be associated with organization and repair of the process in the epicardium and subepicardial myocardium

EXPERIMENTAL PERIPHERAL GANGRENE

EFFECT OF ESTROGENIC SUBSTANCE AND ITS RELATION TO THROMBO-ANGIITIS OBLITERANS

EDWARD J. G. McGRATH, M.D.
Medical Fellow of the National Research Council
CINCINNATI

The present studies have their genesis in an effort to open a new avenue of approach to the problem of thrombo-angiitis obliterans. Perusal of the literature adequately demonstrates the confusion surrounding the clinical and experimental aspects of this disturbance. What knowledge one has concerning the malady has been gleaned from purely clinical and statistical research. Experimental investigation,[1] directed almost exclusively toward establishing a specific bacterial etiologic agent for the disease, has thus far either failed completely or the results have been so meager as to be altogether inconclusive.

It would appear rather facetious to state that in an endeavor to reproduce experimentally a pathologic entity one must first know the pathology. Nevertheless it is here that the first difficulty is encountered. There is no unanimity of opinion among students of the disease regarding the pathology of thrombo-angiitis obliterans. Buerger,[2] in his descriptions of the pathogenicity and chronologic pathology, postulated the following series of events: There is an initial acute inflammation with polymorphonuclear leukocytic invasion of the perivascular tissues and of all the coats of the vessel. Synchronously, thrombosis occurs in the area of inflammation. This is followed by replacement of the inflammatory cells by connective tissue, organization and canalization of the thrombus and finally a great overgrowth of connective tissue in and about the adventitia, binding the artery, the vein and the nerve

From the Laboratory of Surgical Research, the Department of Surgery of the University of Cincinnati College of Medicine.

1. (*a*) Rabinowitz, H. M.: Experiments on the Infectious Origin of Thrombo-Angiitis Obliterans and the Isolation of a Specific Organism from the Blood Stream, Surg., Gynec. & Obst. **37**:353, 1923. (*b*) Buerger, Leo: Thrombo-Angiitis Obliterans: Experimental Reproduction of Lesions, Arch. Path. **7**:381 (March) 1929. (*c*) Horton, B. T., and Dorsey, A. H. E.: Experimental Thrombo-Angiitis Obliterans: Bacteriologic and Pathologic Studies, Arch. Path. **13**:910 (June) 1932.

2. Buerger, Leo: Thrombo-Angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, Am. J. M. Sc. **136**:567, 1908; Is Thrombo-Angiitis Obliterans an Infectious Disease? Surg., Gynec. & Obst. **19**:582, 1914; The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

together. Mahorner,[3] Telford and Stopford [4] and others have expressed the opinion that the earliest pathologic process consists in the invasion of the adventitia by lymphocytes. This change is associated with cellular proliferation of the intima. Subsequently a thrombus forms, completing the occlusion of the vessel. The thrombus becomes organized and canalized, with replacement of the inflammatory cells by connective tissue. This lesion progresses to a fibrous matting together of the artery, vein and nerve. These authors specifically stated that the disease is essentially chronic rather than acute and that intimal proliferation probably precedes the deposition of the thrombus rather than occurring simultaneously with it. Another disputed point is the presence or absence of an increase of elastic tissue in the intima. Still another is the significance of giant cells in the lesion. Buerger spoke of them as characteristic. Other investigators made little mention of them. With regard to the media of the affected vessels, Mahorner noted that the muscle cells are well preserved and rarely show a change except late in the disease, when they may be atrophied and show some increase in interstitial connective tissue. Telford and Stopford remarked that the amount of muscular tissue in the media is much reduced and that the fibers are separated by fibrous connective tissue. Mahorner observed that the internal elastic membrane is not split. Telford and Stopford observed that it was fragmented and fibrillated. So unsettled is the question that Horton and Dorsey [1c] expressed doubt as to whether the lesion of thrombo-angiitis obliterans is a distinct entity and remarked that until this is settled the results of experiments on animals must not be held to be conclusive.

Previous experimenters, in attempts to disclose a specific etiologic agent, took as their pathologic criteria intimal proliferation and thrombus formation, together with gross trophic disturbances in the area distal to and supplied by the occluded vessel.[5] This is true of the work of Rabinowitz [1a] and Horton and Dorsey [1c] and of the observations of Kaunitz [6a] with ergot. These are the two points on which most patholo-

3. Mahorner, H. R., in Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans, Mayo Clinic Monograph, Philadelphia, W. B. Saunders Company, 1928.

4. Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. **2**:1035, 1924.

5. This is not entirely true of the recent work of Schmidt-Weyland (Klin. Wchnschr. **11**:2148, 1932). While these were the major observations, leukocytic infiltration was also evident. His method was somewhat of a departure from the customary methods of experimentation in this field.

6. (*a*) Kaunitz, J.: The Pathologic Similarity of Thrombo-Angiitis Obliterans and Endemic Ergotism, Am. J. Path. **6**:299, 1930; (*b*) Chronic Endemic Ergotism: Its Relation to the Vasomotor and Trophic Diseases, Arch. Int. Med. **47**:548 (April) 1931; (*c*) Chronic Endemic Ergotism: Its Relation to Thrombo-Angiitis Obliterans, Arch. Surg. **25**:1135 (Dec.) 1932.

gists seem to agree, although, as has already been indicated, the sequence of even these two phenomena is still debated.

This review indicates that the actual reproduction of a lesion the pathologic process of which has not been definitely determined is scarcely feasible. On the other hand, if one can produce a lesion comparable to that pathologic process which affects the same system—the vascular tree—and shows on histologic examination changes similar to those in the disease under investigation, one is, I believe, justified in pointing out corollaries in terms of the disease in question. However, it is further necessary that the pathologic process be produced regularly in the experimental animals. As I have previously indicated, attempts to establish such a lesion with bacterial agents have been, at best, suggestive rather than conclusive. Certainly they have not met with a regularity of success which would render any experimental manipulation amenable to a mathematical analysis of the results.

In recent years Kaunitz [6] has emphasized the rather striking similarity, both clinical and pathologic, between ergotism and thromboangiitis obliterans. His development of this theorem is adequately presented and at this time needs no further elaboration. He found that both in acute and in chronic ergot intoxication gangrene was produced. Histologic examination demonstrated definite intimal proliferation, thrombus formation, organization of the thrombus and recanalization. These are all the criteria customarily required by investigators in this field. Whether or not there is such an etiologic relationship between ergot and thrombo-angiitis obliterans as Kaunitz suggested is difficult to say. Certainly I am not desirous of recording myself as subscribing to this theory. Nevertheless, I feel that one may reasonably accept ergot arteritis and ergot gangrene as a typical pathologic process on which to base further studies. The results, while not directly translatable in terms of thrombo-angiitis obliterans, at least suggest possibilities in the ultimate solution of the problem.

Two factors in the procedure of Kaunitz, however, were unsatisfactory for my purposes. He used the cock, the comb of which is not so analogous to the arterial tree in man as is desirable. Moreover, ergot was employed in the form of the whole drug which is not amenable to careful dosage and contains at least four vasotropic substances: histamine, tyramine, choline and its derivatives and the specific alkaloid of the fungus. Fortunately, in 1923, Rothlin,[7] working with ergotamine, the alkaloid isolated from ergot by Stoll in 1918, found that it possessed not only the same physiologic but also the same toxicologic

7. Rothlin, E.: Recherches expérimentales sur l'ergotamine, alcalöide spécifique de l'ergot de Seigle, Arch. internat. de pharmacodyn. et de thérap. **27**:459, 1923.

action as does the whole fungus. He found that albino rats given toxic quantities of ergotamine tartrate showed within from five to seven days thereafter pallor of the end of the tail, followed by marked congestion, the tail becoming blue, then black; finally demarcation occurred, and the distal gangrenous portion dropped off, the proximal stump healing over. Polak,[8] in 1924, experimenting with the gangrene of ergotamine intoxication, found that section of the abdominal sympathetic chains definitely hastened the onset of the gangrene, while the administration of epinephrine markedly delayed the process. Both these investigators found that gangrene of the rat's tail was produced regularly by ergotamine. It is this method—the administration of toxic quantities of ergotamine to white rats—which I adopted for the present studies.

Fig. 1.—Rat's tail sixteen days after an injection of ergotamine.

The experiments of Rothlin[7] were repeated, and the gross phenomena described by him were duplicated. Male and female albino rats weighing from 140 to 170 Gm. were given an intoxicating dose of ergotamine tartrate (gynergen).[9] The drug was administered subcutaneously, the dose varying in successive groups from 25 to 100 mg. per kilogram of body weight. It was found that in the females as well as in the males even the lower limit of these dosages was sufficient to produce gangrene of the tail. Unlike the experience of Rothlin,[7] the pregangrenous changes in my animals did not always occur within from five to seven days. With greater doses of ergotamine pallor of the tail appeared as early as the third day, while cyanosis and gangrene were

8. Polak, E.: Experiments on Ergotism, Časop. lék. česk. **63**:1409, 1924.

9. The gynergen, sandoz, and theelin, Parke, Davis and Co., used in these studies were the standard products, purchased in the open market.

sometimes delayed as late as from the twenty-eighth to the thirty-third day. When demarcation became definite (fig. 1), the animal was anesthetized with ether and the entire tail amputated between ligatures. Sections were taken at various levels.

PATHOLOGY OF ACUTE ERGOTISM

As Rothlin [7] clearly described, the symptoms manifested by the rats immediately following the injection of ergotamine were those of acute intoxication, lasting for about two hours, at the end of which time the animals recovered spontaneously and were to all appearances normal. On from the third to the fifth day (table 1), in proportion to the dose of ergotamine, the end of the tail became pale for a variable distance and was distinctly more sensitive to touch than was the

TABLE 1.—*Mean Day of Onset of the Trophic Changes and Extent of the Gangrene in the Tails of the Four Series* *

	Pallor	Cyanosis	Blackening	Demarcation	Extent of Gangrene, Inches
Series 1.....	4.90	9.36	16.16	20.00	1.72
	±0.117520	±0.151600	±0.434625	±0.464800	±0.068533
Series 2.....	4.45	8.25	12.50	16.20	1.92
	±0.111597	±0.125054	±0.228731	±0.309458	±0.087295
Series 3.....	3.95	7.80	10.80	14.55	1.96
	±0.075022	±0.107707	±0.151445	±0.226105	±0.088804
Series 4†.....	3.00	6.38	9.83	16.16	1.91
	±0.00	±0.342524	±0.473083	±1.932614	±0.107088

* The figures in the first four columns represent the mean day of onset of the indicated trophic disturbance in rats receiving ergotamine only. The figures in the fifth column represent the mean length of the tail involved in the gangrenous process in inches.

† The extent of the gangrene developing in the two rats of series 4 (see text) which received theelin was ⅝ and ½ inch, respectively.

proximal portion. The pallor gradually faded and by the sixth to the ninth day was replaced by marked cyanosis. The rat could still move the tail throughout its entire length and apparently suffered exquisite pain when the affected area was touched. The involved portion soon became black, dry, hard and anesthetic. It was demarcated on from the sixteenth to the twentieth day, and thereafter the distal gangrenous portion sloughed off, leaving a proximal stump, which healed. About the time that cyanosis was pronounced in the tail an area of local necrosis appeared on the back of the animal at the point of injection of the ergotamine. This separated and was ultimately cast off and replaced with new skin.

The predominant histopathologic feature was the marked cellular proliferation and swelling of the intima. This was most evident in the smaller arteries and arterioles, where in some sections the lumens

were almost completely occluded (fig. 2). To some extent the process involved the veins and, to a lesser degree, the large central artery of the tail. In the latter vessel the outstanding pathologic change was the presence of a thrombus (fig. 3). The intima had become adherent to the occluding mass and in places had been drawn completely away from the internal elastic membrane. At other points there seemed to

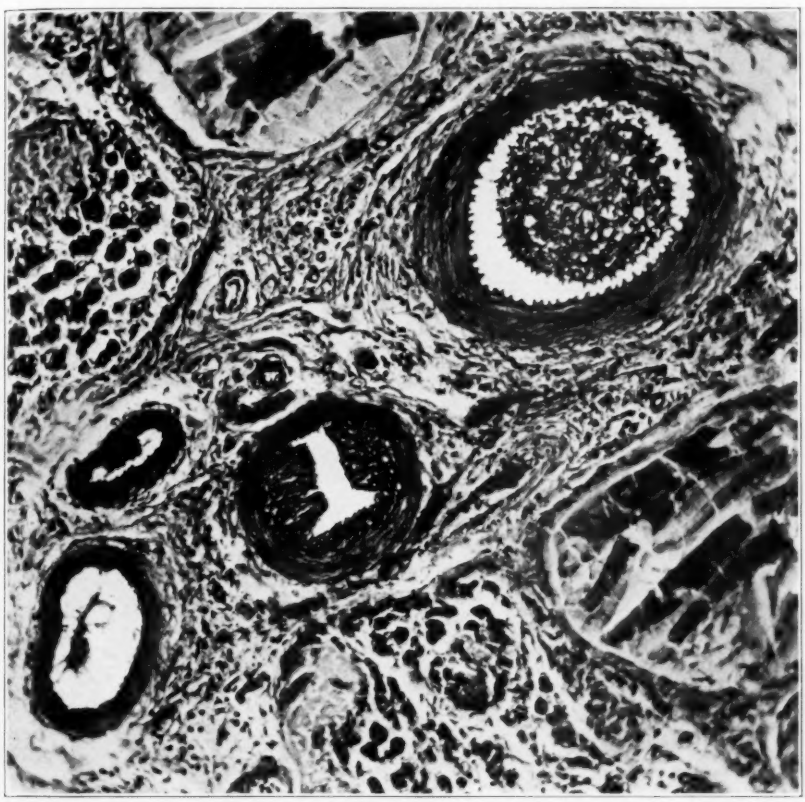

Fig. 2.—Cross-section of the tail showing figure 1. The intima of the central arteriole has proliferated markedly. The large vessel containing the thrombus is the main artery. Magnification, × 200.

be a definite attachment to the wall of the vessel. In sections taken from tails in which demarcation was complete the thrombus had rapidly become organized and canalized (fig. 4), the penetrating channels demonstrating in high power magnification a definite endothelial lining. The internal elastic membrane was intact throughout, and while the muscle cells of the media were usually edematous the

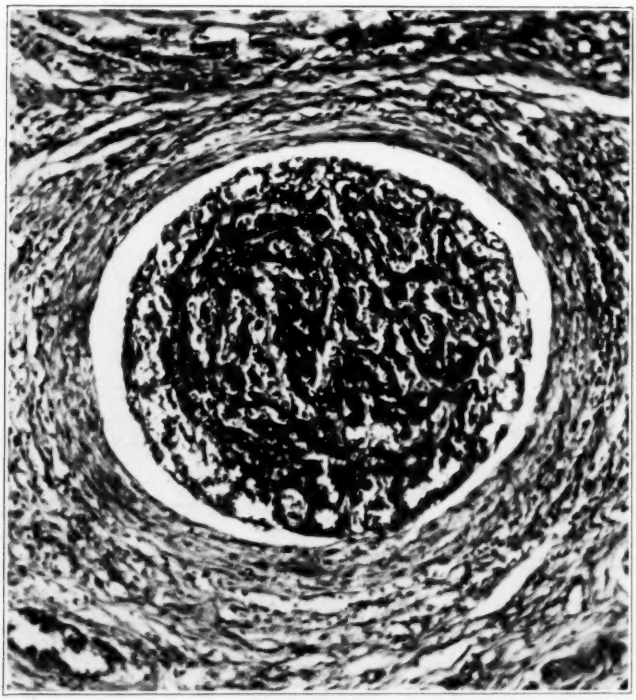

Fig. 3.—Cross-section of the tail, showing the thrombus occluding the central artery. Magnification, × 200.

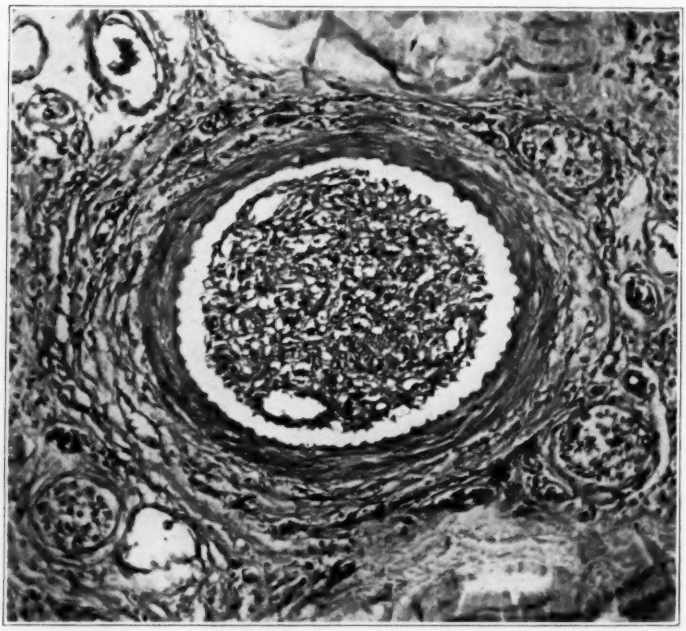

Fig. 4.—Cross-section of the tail, showing the occluding thrombus to have undergone canalization. Magnification, × 200.

characteristic changes present were confined within this barrier. There was no appreciable leukocytic reaction either within the coats of the arteries or arterioles or in the periarterial tissues.

The veins, on the other hand, especially those superficially located, while demonstrating intimal proliferation and thrombosis, in many sections showed in addition marked thrombophlebitis (fig. 5). In those areas the perivenous tissues, as well as the adventitia and the media of the vein and the thrombus were invaded by polymorphonuclear

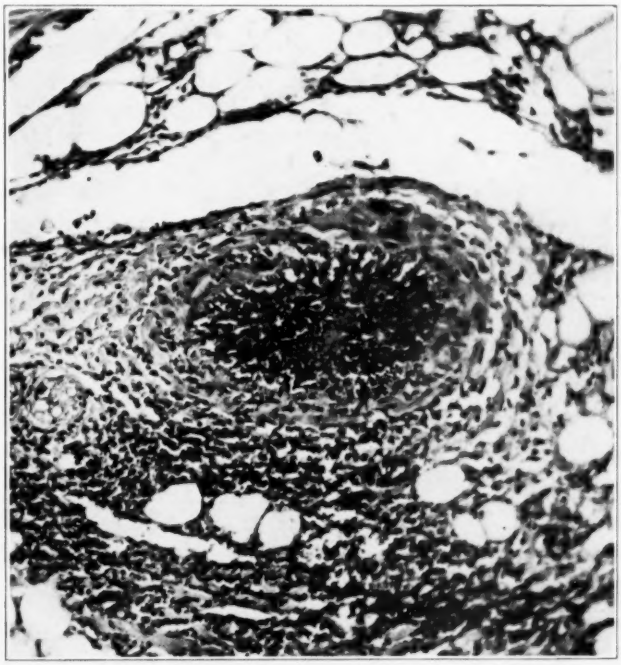

Fig. 5.—Cross-section of the tail, showing the area of thrombophlebitis. The thrombus, the walls of the vessel and the perivenous tissues are invaded by polymorphonuclear leukocytes. Magnification, × 200.

leukocytes. The only noticeable change in the nerves was that in high power magnification there appeared to be vacuolation of the myelin sheaths. Such inflammatory reaction as was present, other than that in the phlebitic areas, was restricted to the zone of demarcation. Here I observed masses of leukocytes, both neutrophilic and lymphocytic, while advancing distally into the inflammatory area were sheets of young fibroblasts. It seems more logical to interpret this reaction as a part of the process of healing than to consider it a response to the irritant.

It is to be emphasized that the changes described occurred in the tail, remote from the site of injection of ergotamine, which in all the animals was on the back, high up toward the shoulders. It is further to be noted that I was dealing with the manifestations of an acute rather than a chronic lesion. Experiments consisting in the protracted feeding of ergot to rats in order to study the lesions of chronic ergotism in these animals are in progress at the present time. For the moment, however, since the purpose was to approach the problem of thrombo-angiitis obliterans from an etiologic angle, I was particularly desirous of approximating the earlier lesions of the disease. With this in mind, two things were important: First, the lesions were produced regularly both in male and in female rats. Second, the microscopic lesions consisted in cellular proliferation of the intima, thrombus formation, organization and recanalization of the thrombus, thrombophlebitis and ischemic or toxic changes in the nerves. These, I believe, warrant the premise that while I have not and do not claim to have reproduced thrombo-angiitis obliterans, nevertheless I produced a pathologic condition which grossly and microscopically is sufficiently analogous to this disease to justify further experimental study.

EXPERIMENTAL STUDIES

Having definitely established the regularity of the production of gangrene in the rat's tail by the use of ergotamine, I proceeded to the immediate problem. Among what appear now to be firmly established facts in the etiology of thrombo-angiitis obliterans, two are outstanding. The first is the deleterious effect of tobacco smoking on the progress of the disease. While the etiologic position of tobacco in thrombo-angiitis obliterans is still a moot point, clinically tobacco is universally indicted,[10] and the clinical-experimental studies of Barker,[11] Maddock and Coller,[12] Harkevy [13] and Sulzberger and his associates [14] seem defi-

10. Meyer, W.: Etiology of Thrombo-Angiitis Obliterans, J. A. M. A. **71**: 1268 (Oct. 19) 1918; A Further Contribution to the Etiology of Thrombo-Angiitis Obliterans, M. Rec. **97**:425, 1920. Silbert, S.: Studies on Thrombo-Angiitis Obliterans (Buerger): II. The Effectiveness of Therapeutic Procedures, J. A. M. A. **89**:964 (Sept. 17) 1927. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans: Further Experiences with Treatment, J. A. M. A. **102**:436 (Feb. 10) 1934.

11. Barker, N. W.: The Tobacco Factor in Thrombo-Angiitis Obliterans, Proc. Staff Meet., Mayo Clin. **6**:65, 1931; Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet., Mayo Clin. **8**:284, 1933.

12. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, Ann. Surg. **97**:70, 1933.

13. Harkevy, J.; Hebald, S., and Silbert, S.: Tobacco Sensitiveness in Thrombo-Angiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **30**:104, 1932.

14. Sulzberger, M. B.; Scholder, B., and Feit, E.: Studies in Tobacco Hypersensitivity, J. Immunol. **24**:85, 1933.

nitely to substantiate the wisdom of this clinical judgment. The results of my own studies with tobacco will be treated in a subsequent publication. The second etiologic factor, probably the more striking, is the almost complete sex limitation of the disease. That the male is the more predominant victim was noted by clinicians [15] almost as early as the disease was identified as a specific clinical entity. Wider recognition of the symptomatology and a somewhat clearer knowledge of the pathology of the process have brought to light a much wider prevalence of thrombo-angiitis obliterans than had previously been suspected. The consequent possibility of compiling statistics demonstrates conclusively that with the exception of isolated instances [16] in most of which the condition was unverified pathologically, the disease is definitely limited to the male. Horton and Brown,[17] reviewing the cases reported up to 1932, offered as a possible answer that women do have the disease, but in a much milder form than that occurring in men, and that the disease in women is overlooked because of the failure of development of the more serious sequelae. Even if this were true, however, the present proportion of less than 2 per cent of cases in women would not be seriously altered. Furthermore, this variation in degree between men and women remains to be explained. Is it possible that such disproportion may be founded on an endocrine basis? Let the question be transposed: translating thrombo-angiitis obliterans in terms of ergot intoxication, what, if any, effect would an excess of available estrogenic substance have on the development of gangrene in the tail of a rat intoxicated with ergotamine?

A series of male and female rats was used, each rat receiving an initial intoxicating dose of ergotamine tartrate (25 mg. per kilogram of body weight), and after an interval of twenty-four hours to allow thorough absorption of the alkaloid from the site of injection the administration of theelin in aqueous solution at the rate of 2 rat units per animal daily was begun. The injections of theelin were continued over a period of thirty days, at the end of which time all changes seemed to have ceased. As a further precaution the animals were observed for an additional twenty days. It was found that: (1) in all rats, both male and female, receiving ergotamine alone, gangrene of the tail developed; (2) in

15. Wwedensky, A. A.: Ueber Arteritis Obliterans und ihre Folgen, Arch. f. klin. Chir. **57**:98, 1898.

16. Meleny, F. L., and Miller, G. G.: A Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. **81**:976, 1925. Telford, E. D., and Stopford, J. S. B.: Two Cases of Thrombo-Angiitis Obliterans in Women, Brit. M. J. **1**:1140, 1927. Trabaud, J., and Mredden, I.: Maladie de Léo Buerger chez une jeune fille musulmane, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:579, 1931.

17. Horton, B. T., and Brown, G. E.: Thrombo-Angiitis Obliterans Among Women, Arch. Int. Med. **50**:884 (Dec.) 1932.

all male rats receiving both ergotamine and theelin gangrene developed comparable in extent to that in the animals receiving no theelin; (3) in female rats receiving both ergotamine and theelin gangrene did not develop; (4) in normal controls, male and female, no disturbances developed (tables 2 and 3).

The experiment was repeated, ergotamine being used in the ratio of 40 mg. per kilogram of body weight, while in view of the results

TABLE 2.—*Results of Tests on the Females in the Four Series* *

	Series 1 Ergotamine, 25 Mg. per Kg.	Series 2 Ergotamine, 40 Mg. per Kg.	Series 3 Ergotamine, 60 Mg. per Kg.	Series 4 Ergotamine, 100 Mg. per Kg.	Total
Number of rats	30	30	30	30	120
Normal controls	10	10	10	10	40
Rats receiving ergotamine alone	10	10	10	10	40
Rats receiving ergotamine and theelin	10	10	10	10	40
Dosage of theelin, rat units daily	2	3	3	5†	
Gangrene in normal controls	0	0	0	0	0
Gangrene without theelin	10	10	10	10	40
Gangrene with theelin	0	0	0	2	2
Deaths	0	0	0	1	1

* Ergotamine was given in a single dose at the beginning of the experiment; injections of theelin were made over periods of thirty days, and the rats were observed for an additional twenty days thereafter.

† Five rat units was the standard dose in series 4. In four rats, because of changes in the tails, 10 rat units was used daily.

TABLE 3.—*Results of Tests on the Male Rats in the First Three Series* *

	Series 1 Ergotamine, 25 Mg. per Kg.	Series 2 Ergotamine, 40 Mg. per Kg.	Series 3 Ergotamine, 60 Mg. per Kg.	Total
Number of rats	30	15	15	60
Normal controls	10	5	5	20
Rats receiving ergotamine alone	10	5	5	20
Rats receiving ergotamine and theelin	10	5	5	20
Dosage of theelin, rat units daily	2	5	8	
Gangrene in normal controls	0	0	0	0
Gangrene without theelin	10	5	5	20
Gangrene with theelin	10	5	5	20
Deaths	0	0	0	0

* Ergotamine was given in a single dose at the beginning of the individual series. The periods of injection of theelin and of observation were synchronous with those in the corresponding series of females, as indicated in table 2.

in males in the preceding experiment the dose of theelin was increased to 3 rat units daily for females and 5 rat units daily for males. The results in this series were identical with those in the previous study. In a third series ergotamine was utilized in the ratio of 60 mg. per kilogram of body weight, with doses of theelin of 3 rat units daily for females and 8 rat units daily for males. Again the results were the same: In all the rats except the females protected by theelin gangrene of the tail developed; in the protected females, no trophic lesions developed.

A fourth series was studied, consisting only of females. Ergotamine was used in doses of 100 mg. per kilogram of body weight. Four rats received ergotamine alone; six were given ergotamine and subsequent daily doses of 1 cc. of physiologic solution of sodium chloride subcutaneously, and ten received the initial injection of ergotamine and thereafter theelin at the rate of 5 rat units daily. In this series it became evident early in the experiment that trouble would be encountered. In all the rats receiving ergotamine alone or accompanied by physiologic solution of sodium chloride, gangrene developed. However, in two of the group protected by theelin, gangrene quickly developed despite all efforts to thwart the process. These lesions, while appearing as early as those in the control group, had less than one-half the extent of those developing in unprotected animals (table 1). Two other animals showed evidence of vascular change in the tail in the form of pallor and mild cyanosis early in the course of the experiment. In these the dose of theelin was immediately doubled and was kept at that level for the remainder of the experiment. The pallor and cyanosis disappeared, and at the end of the study the rats in question could in no way be differentiated from the other animals protected by theelin. Thus in this series also the result was that in all ergotaminized rats unprotected by theelin, gangrene of the tail developed. In two of the animals protected by theelin, gangrene developed, while two others showed early vascular changes which promptly disappeared when the dose of theelin was doubled. The remaining rats demonstrated no changes.

ANALYSIS OF RESULTS

The patent fact derived from these experiments is that female rats previously intoxicated with ergotamine tartrate in amounts sufficient to produce gangrene of the tail were protected from the development of the gangrene by adequate amounts of theelin (table 3). While inspection of the results alone discloses this, the data for this series were subjected to the chi square test of probability.[18] This analysis demonstrates conclusively that the results are not attributable to the operation of chance alone. At first glance it would seem that theelin had no protective action on the male rats of the experiment (table 3). A mathematical analysis of the mean results, however, indicates that in series 1 there was a significant delay in the onset of trophic changes in the male rats receiving theelin as compared with the onset in males

18. Chi square for the females of the four series, contrasting the results in those receiving ergotamine alone with the results in those receiving both ergotamine and theelin, on the basis of the development of gangrene of the tail, was 72.380925, the interpolation of which indicates that the possibility that these results were due to the operation of chance alone is less than 1 in 400,000,000,000.

not receiving theelin. This series was small, and the delay may disappear in a larger group. Moreover, the delay was not encountered in the later series of males. Considering the fact, however, that all the dosages of theelin used in the study were purely empirical, the discovery of this phenomenon in series 1 suggests the possibility that theelin may have some effect on the male, if administered in sufficiently large doses. Experiments testing this hypothesis are in progress.

In table 1 are compiled the mean times of appearance of the major trophic changes—pallor, cyanosis, blackness of the tail and demarcation of the gangrenous portion—together with the mean extent of the gangrenous process in the tails under increasing doses of ergotamine. Analysis of these means indicates a significant increase in the speed with which the trophic disturbances occur, varying directly with the increase of the dose of ergotamine. Such a relationship is not apparent in the extent of grangrene.

COMMENT

The mode of production of gangrene by ergot or its alkaloid, ergotamine, is not entirely clear. Cushny [19] stated that "the gangrene of ergot poisoning arises from the prolonged constriction of the vessels by the ergotoxine and ergotamine." In the next paragraph, however, one finds the statement: "The ergot alkaloids do not act on the inhibitory junctions (of the sympathetic nervous system) at all, and while stimulating the motor myoneural junctions in small doses, paralyze them in large amounts." A similar description of the action of ergot and its alkaloids was offered by Dale,[20] Mendez,[21] Bastido [22] and Solis-Cohen and Githens.[23] The last two offered the following observation:

> [In the cockscomb] There seems to be a contraction of all the vessels, most marked in the finer veins, leading to cyanosis. The vessels are dilated at first, and filled with brownish masses. Later, their walls [of the vessels], and finally the entire thickness of the comb, undergo hyaline degeneration, the vessels being filled with hyaline thrombi. A similar discoloration of the comb is produced by cantharides, which does not cause vasoconstriction, but it is not induced by other vasoconstrictors.

19. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 9, Philadelphia, Lea & Febiger, 1928, p. 400.

20. Dale, H. H.: On Some Physiologic Actions of Ergot, J. Physiol. **34**:163, 1906.

21. Mendez, R.: Antagonism of Adrenalin by Ergotamine, J. Pharmacol. & Exper. Therap. **32**:451, 1928.

22. Bastido, W. A.: Materia Medica, ed. 3, Philadelphia, W. B. Saunders Company, 1933, p. 657.

23. Solis-Cohen, S., and Githens, T. S.: Pharmacotherapeutics, New York, D. Appleton & Company, 1928, p. 1768.

Rothlin [24] expressed the opinion that the action of ergotamine is not on the motor junctions alone but that the inhibitory junctions are also involved. Further, it was stated by Heymans and Regniers,[25] as well as by Ganter [26] that ergotamine has a constant vasodilating effect in addition to its vasoconstricting effect, the one to manifest itself being dependent on the index of epinephrine in the blood at the time. Kaunitz [6e] expressed the belief that the gangrene subsequent to ergot intoxication is due to the dystonic vascular condition; that is, there is a spasm of the arteries with dilatation of their terminal capillaries. He further suggested the possibility that the other amines in ergot, histamine, tyramine and choline may play a rôle in the phenomena observed. This possibility does not, of course, apply in the studies I am reporting, since ergotamine rather than the whole fungus was employed.

The nature of the interaction between the estrogenic factor and ergotamine is little understood. While knowledge of the action of ergotamine in toxic quantities is meager, knowledge of the action of theelin on the vascular system is virtually nil. Recent clinical studies indicate that some connection exists. In an analysis of 1,230 cases, Alvarez and Zimmermann [27] noted that sexually abnormal women have blood pressures that average considerably higher than those of women who are sexually normal and that a masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, thyroid disease and pelvic conditions requiring ovariectomy or hysterectomy are associated with a high average blood pressure. Conversely, Crainicianu and his co-workers,[28] using estrogenic preparations, found that the intravenous injection of 100 rat units in dogs, especially in females, was followed by a drop in the blood pressure. Following the intravenous administration of 100 rat units to 100 human subjects a similar effect was noted, except in castrated women. Aymen,[29] contrariwise, in a careful

24. Rothlin, E.: Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, J. Pharmacol. & Exper. Therap. **36**:657, 1929.

25. Heymans, C., and Regniers, P.: Sur l'action vasculaire et sympathétique de l'ergotamine et de l'ergotinine, Arch. internat. de pharmacodyn. et de thérap. **33**:236, 1927.

26. Ganter, G.: Ueber die Ausschaltung des vegetativen Nervensystems am Kreislauf, Arch. f. exper. Path. u. Pharmakol. **113**:129, 1926.

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study of 10 patients, found that the daily administration of theelin over a period of three months, and in daily doses as high as 350 rat units was without any discernible effect on the blood pressure of hypertensive patients. It should be remarked in this connection, however, that while Alvarez and Zimmermann's study was statistical and was directed at what might be termed naturally existing conditions, Aymen's investigation was directed toward the study of the effect of therapy with theelin on a preexisting pathologic condition. Baecke [30] and Sicard [31] independently reported cases of thrombo-angiitis obliterans in which the patient was relieved by therapy with estrogenic substance. Neither author offered a satisfactory explanation for the mechanism of the therapy. This work has not, to my knowledge, been corroborated by other clinicians. Kaunitz,[6c] reviewed the reports of such early observers as Noel (1710), Tessier (1783), Renauldin (1815) and Krysinsky (1888) and cited their emphasis on the fact that in epidemic ergotism the gangrenous form of intoxication by the fungus failed, for the most part, to manifest itself in women. Such being the status of opinion as to the mode of operation not only of the estrogenic substance but also of ergotamine intoxication on the vascular system, I am forced to content myself at present with a simple record of my results, without offering any explanation of their causation.

The following observed phenomena are stressed:

1. Thrombo-angiitis obliterans has been recognized by investigators to be a sex-limited disease, attacking the male only, or, if one prefers the more conservative view advanced by Horton and Brown, its occurrence in the female is so mild as to escape notice.

2. In my present experiment, considering the gangrenous manifestations of ergotamine intoxication in the albino rat as a typical pathologic process, I found that females receiving sufficiently large doses of theelin are protected from the trophic disturbances which otherwise regularly follow intoxication with ergotamine tartrate.

I do not insist that there is a necessary connection between these phenomena. Nevertheless I think that it is not imprudent to indicate that herein lies the suggestion that in obliterative vascular diseases, notably in thrombo-angiitis obliterans, there may be some underlying dyscrasia, possibly endocrine, and that the absence of or at least the notably milder form of the disease in the female may be associated with a protective action of the ovarian estrogenic factor.

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SUMMARY

The similarity between thrombo-angiitis obliterans and the gangrene of ergotamine intoxication is indicated, and the possibility of accepting the latter as a typical pathologic process on which to make further observations is discussed.

The gangrene of ergotamine intoxication was produced in the albino rat, and the pathologic process is described. The gangrene of the rat's tail can be induced regularly both in males and in females, with sufficiently large doses of ergotamine tartrate.

It was found that there is a significant increase in the speed with which trophic changes occur, varying directly with an increase in the dose of ergotamine tartrate. Such a relationship with regard to the extent of gangrene produced was not apparent in these studies.

The protective action of theelin against the gangrene of ergotamine intoxication was studied in a group of albino rats consisting of forty males and eighty females, exclusive of the normal controls.

Female rats initially intoxicated with ergotamine tartrate were completely protected against the gangrenous sequelae by sufficiently large daily doses of theelin.

In series 1, in which the amount of ergotamine tartrate administered was relatively small (25 mg. per kilogram of body weight), male rats receiving theelin demonstrated a significant delay in the onset of trophic disturbances, as contrasted with male rats not receiving theelin.

The parallelism between the sex limitation of thrombo-angiitis obliterans and the protection of the female rats from ergotamine gangrene by an excess of theelin is indicated.

It was noted that within this parallelism lies the suggestion that there may be in thrombo-angiitis obliterans a basic etiologic disturbance which is possibly endocrine, and that the failure of the disease to manifest itself in women, or at least its presence in a form so mild as to escape clinical notice, may be associated with a protective action of the estrogenic principle of the ovary.

METABOLISM IN UNDERNUTRITION

ITS CHANGES DURING TREATMENT BY HIGH CALORIC DIET

J. M. STRANG, M.D.
Attending Physician

H. B. McCLUGAGE, PH.D.
Biochemist, Institute of Pathology

AND

M. A. BROWNLEE, R.N.
Supervisor of the Metabolic Pavilion

PITTSBURGH

In a recent publication [1] the treatment of undernutrition by high caloric diets was described. During the periods of gain in weight of the patients of the series studied in the hospital, observations were made of the changes which took place in several phases of metabolism. This report describes the observations which were made on the basal metabolism, nitrogen metabolism and efficiency of digestion.

BASAL METABOLISM

Comparatively low levels of basal metabolism have long been recognized in association with undernutrition.[2] The total basal heat output is definitely reduced, and the relative deviations vary somewhat, depending on the use of standards of weight or body surface for the estimation of the basal metabolic rate in view of the unusual body proportions of these patients.[3] The clinical significance which may be attached to observations of low basal metabolic rates is not easily determined. Many reports describe lowered metabolism in association with minor ailments [4] and even in persons with no discoverable pathologic condi-

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From the Medical Service and Institute of Pathology of the Western Pennsylvania Hospital.

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tion.[5] The association of a rapid lowering of the metabolism with an acute loss in weight has been described in starvation [6] and following acute infection.[7] In chronic undernutrition low metabolic levels have been recorded in association with specific diseases, such as diabetes,[3b] and also in less characteristic metabolic disorders.[8] On the other hand, there are many reports of little or no change in the basal metabolism in simple, although chronic, undernutrition,[9] particularly when the observations are expressed in terms of basal metabolic rates.

The mechanism whereby a drop in the level of the metabolism occurs in undernutrition has been much debated. There appears to be no relation between lowering of the basal number of calories produced and lowering of the total body protein or body substance,[10] although low basal metabolism may be associated with a reduction in certain types of body protein.[11] The conception that the lowered level of

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11. Deuel, H. J., Jr.; Sandiford, I.; Sandiford, K., and Boothby, W. M.: Study of Nitrogen Minimum; Effect of Sixty-Three Days of Protein-Free Diet on Nitrogen Partition Products in Urine and on Heat Production, J. Biol. Chem. **76**:391, 1928.

metabolism is due to primary or secondary hypofunction of the several endocrine glands, particularly the thyroid and adrenal glands, has met with considerable opposition.[12] Nor does it appear to be a result of vitamin B deficiency.[13]

The changes in the level of the metabolism which occur following a gain in weight are of particular importance for this study. In general, previous studies have reported definite elevations of the basal metabolism coincident with increases in weight.[14] However, with few exceptions, the rate of increase in weight far exceeds the rate of increase of the metabolism.

The possible effect of the ingestion of large amounts of food per se on the basal metabolism must be kept in mind. Observations have been reported which show an influence of high protein meals from fifteen to eighteen hours after ingestion.[15] The influence of an excessive intake in general on heat production has been much debated, especially the conception of "luxus consumption."[16] Certain authorities, however, believe that the summation effect of the specific dynamic actions of the various food factors explains the increased heat output which follows an increase in food intake[17] and think that there is little or no effect of increased food intake on a truly basal determination.

METHODS

The present report deals with observations of the basal metabolism of undernourished patients before and during treatment by high caloric diets. The patients were under continuous observation in the pavilion for patients with metabolic disturbances. The time intervals for this series of observations differ slightly from those for other observations on the same series of patients. The weights employed were those noted on the morning of the basal determination and therefore differ somewhat from the figures for weight which appear elsewhere.

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15. Lusk, G.[6f] Wishart, G. M.: The Influence of Previous Muscular Activity and Other Factors on the Basal Metabolism, Quart. J. Med. **20**:199, 1926.

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17. DuBois, E. F.[2] Lusk, G.: The Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 388.

The basal metabolism determinations were done at weekly intervals by the Tissot method as a routine at about 7 a. m. The last meal was at 5 p. m. the preceding night, which gave an interval of at least twelve hours before the test. The calculations of the basal metabolic rate were based on the estimated surface area of the body. The normal standards of heat production of DuBois were used throughout.

In any long series of determinations occasional unusual variants are noted. In this series only those values were discarded in which definite technical errors were discovered. When two determinations were carried out in a week the figures recorded for that week are the averages of the two determinations and are so noted in the tables. No period of training could be secured before the institution of the high caloric diets. It is therefore possible that many of the initial determinations are unduly elevated. No basis for the evaluation of this possible error is apparent.

TABLE 1.—*Basal Metabolism Before and After Gain in Weight*

				Initial Observation				Final Observation		
Patient	Age, Years	Sex	Height, In.	Weight, Kg.	Heat Production, Calories per Hour	Basal Metabolic Rate	Weeks	Weight, Kg.	Heat Production, Calories per Hour	Basal Metabolic Rate
1	32	F	64	42.2	49.0	— 5	13	52.5	53.9	— 4
3	32	F	62½	38.6	48.5	+ 1	2	42.6	51.6	+ 2
4	22	F	62	43.1	50.3	— 2	4	46.7	51.4	— 4
5	28	M	66	49.0	54.7	—11	6	53.2	54.9	—14
6	35	M	68	43.0	63.3*	+ 9	6	57.7	77.0*	+16
7	24	F	62	40.8	52.4	+ 4	12	52.6	59.2	+ 6
8	20	F	62½	44.3	46.3*	—11	2	45.1	51.1*	— 5
9	31	F	64¾	47.5	47.9	—13	2	49.3	47.9*	—13
10	23	F	66¼	45.3	49.7*	—10	4	48.1	48.5	—14
11	15	F	59	34.5	41.3	—21	3	36.7	44.3	—18
12	33	F	63	35.6	44.1	— 7	8	42.0	45.2	—11
13	33	F	63	39.5	44.8	—10	3	42.7	45.5*	—11
14	26	F	64¼	50.3	58.4	+ 4	3	53.0	53.0	— 8
15	25	F	67	46.7	64.9	+15	5	51.7	53.0	—10
16	25	F	67	54.8	60.0	— 1	4	57.7	56.5	— 8
17	22	F	64½	47.0	55.4	+ 1	2	48.7	54.1*	— 3
18	33	M	66½	46.7	69.2*	+16	7	54.5	78.3*	+23
Average					52.9	— 2	5		54.4	— 6

* Average of two determinations.

OBSERVATIONS

The observations of the basal metabolism made on seventeen patients at weekly intervals for an average of five weeks are recorded in table 1.

It may be noted that at the outset the average basal metabolic rate for the series was — 2 per cent. The extreme range of values runs from — 21 to + 16 per cent, with eleven of the seventeen values falling between + 10 and — 10 per cent. These rates for undernourished patients correspond favorably with those for any series of normal persons.

If the final observations are compared with the initial observations without regard to duration or to change in weight, the average final heat production was 54.4, as contrasted with 52.9, calories per hour. The increase of 1.5 calories is equivalent to 2.8 per cent of the initial

level. At the same time the increase in weight averaged 5.1 Kg., or 11.5 per cent, in the average period of five weeks. Individual subjects showed changes ranging from a drop of 11.9 calories per hour, with consequent lowering of the basal metabolic rate of 25 per cent in three weeks, to an increase of 13.7 calories per hour and of the basal metabolic rate of 7 per cent in six weeks. Eleven patients showed an increase in heat production, which was in most cases very slight and in four patients so small that the basal metabolic rate was reduced owing to the simultaneous increase in body surface. Five patients showed a lower caloric output after an increase in weight and in consequence a much lower basal metabolic rate. The detailed weekly observations of the basal metabolism have been omitted.

The object of the present study is to note the metabolic changes which accompanied changes in weight. The majority of our series of

TABLE 2.—*Metabolism Changes of Patients Who Gained Five Kilograms or More*

	Heat Production, Calories per Hour			Body Surface, Sq. Meters			Basal Metabolic Rate Actual Body Surface			Basal Metabolic Rate Ideal Body Surface		Change in Weight	
Patient	Initial Observation	Final Observation	Percentage of Increase	Initial Observation	Final Observation	Percentage of Increase	Initial Observation	Final Observation	Ideal Body Surface, Sq. Meters	Initial Observation	Final Observation	Kg.	Percentage
1	49.0	53.9	10	1.41	1.54	9	— 5	— 4	1.64	—18	—10	10.3	24
6	63.3	77.0	22	1.49	1.69	13	+ 9	+16	1.84	—13	+ 5	14.7	34
7	52.4	59.2	13	1.37	1.51	10	+ 4	+ 6	1.55	— 9	+ 3	11.8	29
12	44.1	45.2	2	1.30	1.39	7	— 7	—11	1.61	—25	—23	6.4	18
15	64.9	53.0	—18	1.53	1.59	4	+15	—10	1.72	+ 2	—17	5.0	10
18	60.2	78.3	13	1.52	1.63	7	+16	+23	1.77	— 2	+12	7.8	17
Average	57.1	61.1	7	1.44		8	+ 5	+ 3		—11	— 5	9.3	22

patients did not remain in the hospital long enough to show important changes in body weight or surface. If only those patients who gained 5 Kg. or more are considered, much more striking figures are obtained.

The six patients under consideration gained an average of 9.3 Kg. —an increase of 22 per cent over the initial weights—in 8.5 weeks. The average increase in body surface was 0.12 square meters, or 8 per cent. The initial heat production averaged 57.1 calories per hour, which corresponds to an average basal metabolic rate of + 5 per cent. The final rate of heat production averaged 61.1 calories per hour. The increase of 4 calories corresponds to 7 per cent of the initial level. The average increase in body surface was 8 per cent; hence the change in the basal metabolic rate was very slight. The observed increase in heat production, therefore, practically parallels the increase in body surface, while it is only one third of the increase in weight.

From these data it might be considered that the increase in the metabolic level is influenced primarily by the body surface. The possibility exists of an influence due to the great increase in the food intake

of these patients. The caloric intake for the several weeks has been reported elsewhere.[18] Certain of the figures for patients 1, 3, 10, 13 and 16 might be interpreted to indicate a fluctuation of metabolism with the food intake. The data for patients 9, 12, 15 and 18 could be interpreted as evidence either for or against such a fluctuation. The negative position is, however, clearly defined in the figures for patients 4, 5, 7, 14 and 17, which indicate a complete absence of relation between the caloric intake and the basal metabolism.

Similarly, the data for the protein intake, the total weight of intake, the total nitrogen metabolism, the level of the nitrogen metabolism, the total amount of nitrogen stored and the rate of storage of nitrogen were analyzed with respect to observed changes in heat production. The

TABLE 3.—*Respiratory Quotients*

Patient	Ratio of Fatty Acid to Dextrose of Diet	Weeks												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1	0.61	0.730	.....	.....	.....	0.824	.....	0.891	.....	0.909	0.880	0.852	.....	0.865
3	0.68	0.822	0.795	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
4	0.63	0.760	0.880	0.842	0.902	.....	.....	.....	.....	.....	.....	.....	.....	.....
5	2.44	0.710	0.744	0.780	0.770	0.740	0.740	.....	.....	.....	.....	.....	.....	.....
6	0.69	0.908	0.958	1.000	0.930	0.956	0.923	.....	.....	.....	.....	.....	.....	.....
7	0.61	0.890	0.836	0.927	0.798	0.874	0.883	0.864	0.872	0.908	0.892	0.882	0.868	.....
8	....	0.880	0.870	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
9	0.65	0.826	0.837	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
10	0.84	0.883	0.865	0.792	0.821	.....	.....	.....	.....	.....	.....	.....	.....	.....
11	....	0.814	0.902	0.820	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
12	2.20	0.807	0.798	0.772	0.782	0.771	0.861	0.717	0.797	.....	.....	.....	.....	.....
13	3.19	0.713	0.731	0.752	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
14	0.68	0.820	0.850	0.835	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
15	0.75	1.000	0.788	0.820	0.808	.....	.....	.....	.....	.....	.....	.....	.....	.....
16	0.84	0.968	0.852	0.870	0.818	.....	.....	.....	.....	.....	.....	.....	.....	.....
17	0.65	0.760	0.855	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
18	0.72	0.796	0.884	0.910	0.830	0.810	0.750	0.785	.....	.....	.....	.....	.....	.....

detailed data have not been included in this report, but it may be stated that no relationship could be detected between these factors and their fluctuations and the changes in heat production.

The respiratory quotients which were observed are recorded in table 3.

There was a general tendency toward slightly higher values than are usually found for a similar series of normal persons. Characteristic changes in the respiratory quotients will be noted in the six patients who were studied for six weeks or longer.

In view of the many publications which describe the influence of the diet on the respiratory quotient, the figures for the fatty acid-dextrose ratio for the several patients are given (table 3, column 2). Patients 5, 12 and 13 were given high fat diets. The quotients for

18. Strang, J. M., and Cox, A. B.: Analysis of High Caloric Diets in Relation to Weight Changes, Ann. Int. Med. **7**:152, 1933.

these patients are definitely below those for the other subjects. It is, however, of interest that in patient 12 the respiratory quotient hovered around 0.8 while she received a diet containing 3,310 calories, with only 9.5 per cent from carbohydrate and 5.7 per cent from protein. Patient 13 had an average intake of 3,450 calories, with 5.3 per cent from protein and 4.8 per cent from carbohydrate. During the third week on this program the respiratory quotient was 0.752. In the remaining subjects the fatty acid-dextrose ratios of the diets ranged from 0.55 to 0.84. In these diets carbohydrate supplied from 27 to 36 per cent of the calories; and fat, from 54 to 66 per cent. The average total calories of all the diets was 3,320, which has been estimated as approximately 35 per cent above the total energy requirement for a day.[18] Also, it was estimated that of the weight gained, approximately one fourth was protein tissue and three fourths fatty tissue.[18] In view of the type of food and the probable nature of the weight gained, the general levels of the respiratory quotients are of especial interest. When the fat content of the diet is pushed to 85 per cent of the total calories, there appears to be slightly increased fat metabolism. A few patients appear to have utilized a relatively high percentage of carbohydrate. Patient 6 had the only consistently high respiratory quotient, and he ingested daily 5,090 calories derived in part from 399 Gm. of carbohydrate and 326 Gm. of fat. In the average diets, however, in which both carbohydrate and fat were given in amounts well over 200 Gm. per day, the source of basal energy does not appear to differ greatly from the normal.

COMMENT

The initial observations made on this series of undernourished patients indicate that the basal metabolism falls within the limits of normal in proportion to the body surface. This fact is reflected in the observation of an average initial basal metabolic rate of —2 per cent ± 8 per cent. The absolute heat production for the same patients was, however, lower than if their weight had been normal. Eight patients produced less than 50 calories per hour, the minimum being 41 calories per hour. A measure of this depression of rate is afforded by the calculation of the basal metabolic rates with the use of the ideal body surface in place of the actual body surface. By this form of expression it is seen that five patients had rates below —20 per cent, and the average for the group was —15 per cent, in contrast to the —2 per cent already noted. It should, however, be clearly recognized that this calculation is not advanced as evidence contravening the principles underlying the standard methods of expression of the relative heat production. The chief merit of the calculation is that it affords one measure of the economy of energy exchange which prevails in undernourished persons. These observations support the conception of a

protective mechanism exhibited by a starved or undernourished body, which has been described by Lusk.[6e]

The dietary treatment of undernutrition appears to exert a definite influence on the level of the basal metabolism. When all the patients are considered, the effect is obscured by the relative preponderance of the short periods of observations. If only those subjects are considered in whom important changes in weight occurred, the change in the basal level becomes more sharply defined. With the exception of one patient, whose initial level was unusually high, there was a distinct tendency for the metabolism to rise with an increase in body mass. The averages indicate that the rise in the level of the metabolism does not parallel the rate of the gain in weight, but is rather of the same order of magnitude as the rate of increase of the body surface.

An opinion which is frequently encountered is that undernourished persons show an increase in the level of the metabolism as a result of forced feeding. Although the food intake of all the persons in the series was increased abruptly, the average basal heat production of the group as a whole was changed but slightly, owing to the insignificant changes in heat production in the subjects studied for short periods. When the six patients who showed a significant change in weight are considered, the elevation of the basal metabolism appears to parallel the increase in body surface and does not follow the marked increase in food intake. The principle of a luxus consumption, therefore, does not appear to be applicable to the basal metabolism. Reference may be made to the estimations of the total heat output which were made for this series of patients.[18] In these calculations the only extra heat influence which was attributed to the excess food intake was the additional specific dynamic action of this excess food. As may be noted, the estimated gains in weight, which were dependent on this calculated total energy output, closely approximated the observed increases in weight. Our data could be interpreted in support of the statement of Lusk [19] that the heat loss in luxus consumption is essentially the additional specific dynamic action of the extra food intake.

Elevation of the basal metabolism has been attributed both to large meals and to high protein meals. Our observations have no bearing on the question of the influence of high protein meals, as our patients uniformly received moderate amounts of protein. With respect to large meals, our data fail to show that a significant elevation of the basal metabolism occurred immediately after the institution of diets furnishing from 3,000 to 5,000 calories daily. The observed changes developed more slowly. In this connection, attention may be called to the observations of the respiratory quotients. The intrinsic dangers of a discus-

19. Lusk, G.,[6f] p. 53.

sion and analysis of the respiratory quotients, especially of untrained subjects, are admitted. However, our subjects were tested under perhaps the most favorable circumstances and in most instances were thoroughly trained before the end of their stay in the hospital. The fact that the respiratory quotients, certainly in the later weeks, did not differ from those of a series of normal persons, suggests that the food influences in the basal state were no greater than in a series of normal persons. Our evidence is rather that the ingested food is promptly and efficiently handled by the gastro-intestinal tract, and that no residue is present to exert a specific dynamic action twelve hours after the evening meal. These observations are in harmony with the conclusions as to gastro-intestinal efficiency that were derived from the study of the fecal output.

NITROGEN METABOLISM

The relationships which exist between the protein metabolism and proper nutrition have been subject to many investigations. The level of the protein intake necessary for adequate nutrition has been much debated. Low,[20] adequate [21] and optimum [22] protein diets have their advocates. Successful nutrition is apparently possible over a wide range of protein intake.[20a] Studies of undernutrition,[23] however, have indicated the association of a depressed protein metabolism with undernourished states.

METHODS

In the observations here reported the nitrogen intake was estimated from the weights of the several foods. The figures for the protein content were based, for the most part, on the analyses of Atwater and Bryant [24] and a few unpublished analyses of our own. The figures recorded in the tables are the average intakes for the respective weekly periods.

The methods for the collection and storage of the urine and feces have been described elsewhere.[25] Aliquot portions of the thoroughly mixed seven day collections of urine and feces were analyzed in duplicate by the macro-Kjeldahl method. Except where specifically noted, all the analyses recorded in the tables are expressed in terms of grams of nitrogen per day for the several weekly

20. (*a*) Mitchell, H. H.: The Physiological Effects of Protein, J. Nutrition **1**:271, 1929. (*b*) Susskind, B.: Ein Stoffwechselversuch bei knapper Ernährung, Ztschr. f. d. ges. exper. Med. **72**:119, 1930.

21. Rubner, M.: Ueber den niedrigsten Eiweissverbrauch, Ztschr. f. d. ges. exper. Med. **72**:99, 1930.

22. Slonaker, J. R.: The Effect of Different Per Cents of Protein in Diet, Am. J. Physiol. **97**:15, 1931.

23. DuBois, E. F.: The Control of Protein in the Diet, J. Am. Dietet. A. **4**:53, 1928. Lusk, G.[6e]

24. Atwater, W. C., and Bryant, A. P.: The Chemical Composition of American Food Materials, U. S. Dept. Agric., bull. 28, 1906, p. 19.

25. Strang, J. M.; McClugage, H. B., and Evans, F. A.: The Nitrogen Balance During the Dietary Correction of Obesity, Am. J. M. Sc. **181**:336, 1931.

periods. For one patient (15) analyses of the stool were made for only four of the five weeks of observation; the average figure observed for the feces of the first four weeks was used in the estimation of the total nitrogen output for the fifth week. No correction of the average data for the variation in the individual periods of observation was attempted, although the periods ranged from three to fourteen weeks. The body weights employed in the calculations are the averages of the initial and final weights, except where otherwise noted.

OBSERVATIONS

The average daily nitrogen intake for the series of eight patients was 10.96 Gm. per day. According to the usual practice, an intake of 1 Gm. of protein per kilogram of ideal weight was ordered. The total nitrogen intake varied from 6.85 to 18.48 Gm. per day, and the intake per kilogram of ideal weight ranged from 0.115 to 0.259 Gm., with an average value of 0.172 Gm. The figures for the individual

TABLE 4.—*Average Daily Nitrogen Exchange*

	Intake				Output				
Patient	Number of Weeks	Total	Per Kg. of Actual Weight	Per Kg. of Ideal Weight	Urine	Feces	Total	Per Kg. of Actual Weight	Per Kg. of Ideal Weight
1	14	6.85	0.144	0.115	4.68	0.99	5.67	0.119	0.095
5	6	9.25	0.178	0.144	7.64	0.66	8.30	0.160	0.129
6	6	18.48	0.368	0.259	8.65	2.13	10.78	0.214	0.151
10	4	8.93	0.193	0.149	6.71	0.89	7.60	0.164	0.127
14	3	11.20	0.215	0.193	8.14	1.53	9.67	0.186	0.166
15	5	8.90	0.179	0.142	4.91	1.30*	6.21	0.125	0.099
16	4	10.00	0.177	0.160	6.92	1.17	8.09	0.143	0.129
18	7	14.06	0.276	0.211	11.29	2.02	13.31	0.261	0.200
Average	6	10.96	0.216	0.172	7.37	1.34	8.70	0.171	0.137

* Average for four weeks.

weekly intakes, which are not included in this table, show some variation from week to week, although the majority of patients maintained a fairly uniform level throughout their stay. Certain patients whose initial level of intake was low showed no increase in this level, even after many weeks. Other patients showed the desired levels in the beginning, which continued. One subject showed an increase in nitrogen intake of from 9 to 15.5 Gm. in four weeks, after which no increase in intake was permitted because of his failure to store nitrogen. The maximum intake was 18.48 Gm., or 0.368 Gm. per kilogram, with a range of variation of from 18 to 18.9 Gm. in six weeks.

The average total output of nitrogen in this series was 8.7 Gm. per day. The extremes of variation were 5.67 and 13.31 Gm. Three patients showed no significant change in the average daily output during their entire stay. In two patients there was a drop in output of 20 per cent in fourteen weeks and 13 per cent in four weeks, respectively. Another patient showed a rise of 17 per cent in output. In one patient (6) the output rose from 8.86 to 12.49 Gm. in five weeks, but never

equaled more than two thirds of his high intake. In patient 18, who had a thyrotoxic condition, the output of nitrogen differed from that of the other patients in that it rose sharply in four weeks to balance the intake at 16 Gm. per day. On the average, the nitrogen output was about 80 per cent of the intake, with a range of from 59 to 95 per cent.

An expression of the output of nitrogen with reference to the body weight may be regarded as the level of the nitrogen output. The average level for the entire series was 0.172 Gm. per kilogram of actual weight, with a range of from 0.119 to 0.261 Gm. With reference to the ideal body weight this value becomes 0.137 Gm. per kilogram.

The changes in the level of output with change in weight are of considerable interest. Of the six patients with moderate outputs, two showed no alteration in the level because the rate of increase in weight paralleled a slight increase in the nitrogen output. Four patients showed a drop which in one case, in which a large increase in weight accompanied a decrease in the total output, amounted to 37 per cent of the initial level. Patient 6, who exhibited a 40 per cent rise in the total output in five weeks, showed no change in the level because of an equivalent large gain in weight. Patient 18 showed a marked relative increase in the nitrogen output—from 0.17 to 0.28 Gm. per kilogram of body weight—in spite of a gain in weight of 9.1 Kg.

COMMENT

Many instances of a low protein intake associated with undernutrition have been reported.[23] An attempt was made to determine the approximate nitrogen intake of several of our subjects which obtained prior to the period of treatment. The figures obtainable were undoubtedly influenced by the residence in the hospital and therefore probably fail to indicate exactly the preexisting intake. Nevertheless, a distinct impression was received that many of our patients had been securing inadequate amounts of protein prior to the periods of study.

The amount of dietary protein necessary for the treatment of undernutrition obviously is related to the total diet. In the treatment of undernourished children amounts varying from 1.1 [26] to from 2 to 4 Gm.[27] per kilogram of body weight have been used, with considerable success. The majority of our patients were given 1 Gm. of protein, or 0.16 Gm. of nitrogen, per kilogram of ideal weight. The average

26. Parsons, J. P.: Nitrogen Metabolism of Children, Am. J. Dis. Child. **39**:1221 (June) 1930.

27. Wang, C. C.; Hawks, J. E., and Kaucher, M.: Metabolism of Undernourished Children: VII. Effect of High and Low Protein Diets on the Nitrogen and Caloric Balance of Undernourished Children, Am. J. Dis. Child. **26**:1161 (Dec.) 1928.

actual intake closely approximated this figure. It may be noted that this average figure is about 30 per cent higher (0.21 Gm. per kilogram) when based on the actual weight. It would appear, therefore, that our patients, on the whole, were on diets of moderate nitrogen content, in fact, somewhat less than that in other series which have been reported.

The absorption and utilization of nitrogen by the gastro-intestinal tracts of undernourished patients is apparently normal, provided that the remaining dietary factors are properly controlled.[28] However, an important loss of nitrogen in the stools has been reported in undernourished subjects under unfavorable conditions.[29] The details of our studies of nitrogen absorption are given later, but it may be stated at this point that no abnormality of this factor was detected in our series.

The total daily nitrogen output of our patients both at the outset and after periods of dieting was definitely below that found in persons of normal weight.[30] Our observations provide no evidence of a waste of nitrogenous material as an explanation of the development or persistence of undernourished states. They tend to show the protective mechanism of starvation (Lusk) with respect to the nitrogen metabolism. If the change in weight is reversed and undernourished patients are fed, is this mechanism reversed? A number of studies bearing on this point [31] indicate that the rise in the nitrogen metabolism following an increase in intake is much delayed and is of a much smaller magnitude than the rise in the intake. The results in our patients were consistent with this experience. Not only was the caloric intake increased by 50 per cent or more, but the nitrogen intake remained, on the average, 25 per cent greater than the output. The majority of patients exhibited little or no increase in the nitrogen output over the

28. (*a*) Coleman, W., and DuBois, E. F.: The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, Arch. Int. Med. **14**: 168 (Aug.) 1914. (*b*) DuBois, E. F.: The Absorption of Food in Typhoid Fever, ibid. **10**:177 (Sept.) 1912. (*c*) Wang, C. C.; Hawks, J. E., and Hays, B. B.: Metabolism of Undernourished Children: V. Protein Metabolism, Am. J. Dis. Child. **35**:968 (June) 1928. (*d*) Whitacre, J.; Willard, A., and Blunt, K.: The Influence of Fiber on Nitrogen Balance and on Fat in the Feces of Human Subjects, J. Nutrition **2**:187, 1929.

29. Rubner, M., quoted by Lusk, G.[6e]

30. Beard, H.: Protein Intake of Medical Students, Am. J. Physiol. **82**:577, 1927. Dennis, W., and Borgstrom, P.: A Study of the Effect of Temperature on Protein Intake, J. Biol. Chem. **61**:109, 1924.

31. (*a*) Van Hoesslin, H., quoted by Lusk, G.[6e] (*b*) Boothby, W. M., and Bernhardt, H.[6b] (*c*) Rubner, M.: Ueber den Stoffwechsel bei Unterernährung, Ztschr. f. d. ges. exper. Med. **72**:123, 1930. (*d*) Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.[9a] (*e*) Deuel, H. J., Jr.; Sandiford, I.; Sandiford, K., and Boothby, W. M.[11] (*f*) Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930.

several weeks of study. The single variant from the general pattern (in patient 18) possibly is due to the underlying pathologic condition, thyrotoxicosis.

The nitrogen metabolism as reflected by the level of the nitrogen output was relatively low in the majority of the patients in our series, averaging 0.13 Gm. per kilogram of ideal weight or 0.16 Gm. per kilogram of actual weight. Many reports have appeared which discuss the minimum level that may be obtained. The influence on the minimum level of the total caloric intake has been well established by studies of both starvation [6f] and underfeeding.[9a]

The minimum "wear and tear" nitrogen was estimated many years ago as 0.044 Gm. per kilogram of body weight.[29] Levels of 0.024 Gm. have been maintained for short periods.[11] According to certain studies of American diets,[30] the normal nitrogen exchange is about 0.16 Gm. per kilogram of ideal weight (in these subjects, the observed weights). In comparison with these standards, our subjects showed levels far above the minimum but at the same time somewhat lower than their ideal nitrogen exchange.

The marked capacity of undernourished subjects for storing nitrogen has been repeatedly described.[32] The avidity for storing nitrogen appears to bear some relation to the degree of undernutrition.[33] However, it is important to maintain an adequate caloric intake as well as an increased nitrogen intake in order to produce this phenomenon. In fact, in many reports it is not possible to distinguish between the influence of feeding increased amounts of protein and that of an increased caloric intake. All the patients of this series had a positive nitrogen balance. On the average, they stored 2.26 Gm. per day. Although the extremes ranged from 7.7 to 0.75 Gm., the majority stored from 1 to 3 Gm. per day. It is noteworthy that although they received only moderate amounts of protein, yet they maintained a relatively large positive nitrogen balance because the output increased but little over the initial level.

The rate of storage of nitrogen does not appear to be related directly to the level of the nitrogen intake. The amounts stored varied from 5 to 41 per cent (average, 19 per cent) of the nitrogen taken in, but bore no direct relation to the magnitude of the intake. Obviously the caloric intake has some influence on the nitrogen storage. However, this relationship is not susceptible of simple expression, either in terms of the amount of nitrogen stored per hundred calories of total intake

32. (*a*) Boothby, W. M., and Bernhardt, H.[6b] (*b*) Lusk, G.[6e] (*c*) Van Hoesslin, H., quoted by Lusk, G.[6e] (*d*) Wang, C. C.; Hawks, J. E., and Kaucher.[27] (*e*) Rubner, M.[31c]

33. Rubner, M.[31c] Van Hoesslin, H.[32c] Wang, C. C.; Hawks, J. E., and Kaucher, M.[27]

or in terms of the amount stored per hundred extra calories of intake.[18] With respect to the body mass, it may be seen that the nitrogen was stored at the average rate of 0.045 Gm. per kilogram per day. Again the rate of storage did not parallel the size of the patient or the degree of undernutrition.

In contrast to the preceding discussion of the rate of nitrogen storage, it is of interest to note the change in the total nitrogen content of

TABLE 5.—*Relative Amount of Nitrogen Stored*

Patient	Nitrogen Stored per Day, Gm.	Ratio of Nitrogen Stored to Nitrogen Intake, Gm.	Caloric Intake	Nitrogen Stored per 100 Calories of Intake, Gm.	Excess Calories*	Nitrogen Stored per 100 Excess Calories, Gm.	Nitrogen Stored per Kg. of Actual Weight, Gm.	Average Kg. Underweight	Nitrogen Stored per Kg. Underweight, Gm.	Average Percentage Underweight	Ratio of Nitrogen Stored to Percentage Underweight, Gm.
1	1.18	0.17	2,760	0.042	614	0.19	0.025	12.2	0.10	21	0.056
5	0.95	0.10	2,980	0.031	897	0.10	0.018	12.5	0.08	20	0.047
6	7.70	0.41	5,090	0.152	2,315	0.33	0.153	21.1	0.37	30	0.260
10	1.33	0.15	3,200	0.044	1,206	0.11	0.029	13.1	0.10	22	0.060
14	1.53	0.13	3,060	0.050	911	0.16	0.029	6.0	0.26	11	0.139
15	2.69	0.30	3,260	0.082	1,022	0.23	0.054	12.9	0.21	22	0.122
16	1.91	0.19	3,310	0.057	1,078	0.18	0.034	6.0	0.32	10	0.191
18	0.75	0.05	4,790	0.016	1,976	0.04	0.015	15.7	0.05	24	0.031
Aver.	2.26	0.19		0.059		0.17	0.045		0.18		0.110

* Strang and Cox.[18]

TABLE 6.—*Total Amount of Nitrogen Stored*

Patient	Number of Days	Nitrogen Stored per Day, Gm.	Total Increase in Nitrogen, Gm.	Initial Nitrogen Content of Body, Gm.	Percentage of Increase of Body Nitrogen	Increase in Body Weight, Kg.	Nitrogen Stored per Kg. of Weight Gained, Gm.	Total Protein Tissue Formed, Kg.	Ratio of Protein Tissue to Weight Gained, Percentage
1	95	1.18	112.1	1,260	8.8	11.4	9.8	2.8	24
5	42	0.95	39.9	1,490	2.6	4.8	8.3	1.0	21
6	42	7.70	323.4	1,240	26.0	17.7	18.2	8.1	45
10	28	1.33	37.2	1,340	2.8	4.3	8.6	0.9	22
14	21	1.53	32.1	1,480	2.1	5.4	5.9	0.8	15
15	35	2.69	94.2	1,400	6.7	6.2	15.2	2.4	38
16	28	1.91	53.5	1,620	3.3	4.9	10.9	1.3	27
18	49	0.75	36.8	1,390	2.6	9.1	4.0	0.9	10
Average	43		91.1	1,400	6.6	8.0	10.1	2.3	25

these patients. The total additions of nitrogen, obtained by multiplying the average amount stored daily by the number of days, appears in column 4 of table 6. On the average, our patients stored 91 Gm. in forty-three days. The maximum amount stored was in patient 6, who retained 323 Gm. of nitrogen in forty-two days. This patient may be compared with the patient described by Lusk,[6e] who stored 124 Gm. in four weeks. Lusk estimated that for 1 Kg. of average body weight the nitrogen content is 30 Gm. On the basis of this estimation, our series of patients had initial nitrogen contents ranging from 1,240 to

1,620 Gm., with an average of 1,400 Gm. The observed increase in the nitrogen content, therefore, constitutes, on the average, 7 per cent of the initial nitrogen content, with a variation of from 2 to 26 per cent.

The relation of the increase in body nitrogen to the increase in weight is recorded in column 8 of table 6. It may be noted that while the patients stored 91 Gm. of nitrogen they gained 8 Kg. One kilogram of the weight gained corresponds to but 10 Gm. of nitrogen, in contrast to the figure of Lusk. This observation may be interpreted to suggest that in the weight gained the proportion of fat to protein is far in excess of the relative amounts of these substances in the average body—a point of view which is in accord with everyday experience, as well as with calculations which have been reported elsewhere.[18] Furthermore, if it is assumed that protein tissue contains 25 per cent solids and 75 per cent water, 1 Gm. of nitrogen corresponds to 25 Gm. of protein tissue. On the basis of these assumptions, the weight gained by our patients as a whole was composed of 75 per cent fat and 25 per cent protein tissue. In individual cases the proportion ranged from 10 to 45 per cent protein and from 55 to 90 per cent fat. It might be stated, therefore, that, whereas in patients 14 and 18 the weight gained was chiefly fat tissue, in patient 6 roughly half of the weight gained was protein tissue.

SUMMARY

Observations on undernourished patients afforded no evidence that nitrogen is dissipated by any peculiar mechanism of nervous, hormonal or other origin. The data indicate a normal or even conservative handling of nitrogenous substances. The total nitrogen output tended to be distinctly lower than the values encountered in a series of patients of normal weight. In proportion to the actual weight of the subjects, the nitrogen levels were within the limits of normal.

In the course of dietary treatment, although the nitrogen intake was not particularly large, the patients stored nitrogen avidly. The nitrogen content of the patients increased by 7 per cent in the relatively short period of six weeks. Of greater importance, however, is the fact that even after long periods of a positive nitrogen balance the level of the nitrogen output did not rise. These observations serve to emphasize the teaching of Rubner and Lusk relative to the great capacity for nitrogen storage which is associated with serious grades of undernutrition.

The rate at which nitrogen is stored by any given subject does not appear to be predictable. In our series of patients no simple relationships could be noted between the rate of storage and the several factors of the total intake, nitrogen intake, nitrogen output, degree of undernutrition or change in weight.

EFFICIENCY OF DIGESTION

In the treatment of undernutrition by high caloric diets it is of importance to determine the utilization of the ingested food. According to many popular notions, thin persons are unable to handle large quantities of food. Functional abnormalities of the gastro-intestinal tract have been noted in association with undernutrition.[34] However, several studies have been reported which showed a normal capacity of the gastro-intestinal tract for handling large food intakes in both acute and chronic forms of undernutrition.[35] The opinion has been stated that it is not possible to overtax the efficiency of the digestive system and that the handling of a food intake regulated by the appetite is no better than that with forced feeding.[36] The observations here recorded in which the relation of the feces to food is employed as the index of digestive efficiency were made on nine patients during their several periods of gain in weight by means of high caloric diets.

METHODS

The methods of determining the food intake have been described elsewhere.[18] Stools were collected in bed pans separate from urine. When the specimens were mixed, the fluid portion was immediately removed and regarded as urine. The feces were transferred to previously weighed wax cartons, which were kept in a refrigerator. The total collection for each twenty-four hours was weighed on a balance to the nearest gram. The twenty-four hour specimens were transferred daily to the laboratory, where they were stored for seven days. Some loss of water through the wax paper occurred in this period; hence the calculations of the total weight and water content are based on the original records of weight determined in the ward. The dates for the collection of feces correspond to those for food intake. It is recognized that this procedure admits a certain lack of correspondence between feces and food. The error, however, is practically negligible in view of the use of seven day averages and of the relative uniformity of the diet from week to week.

Analyses were performed on aliquot portions of the thoroughly mixed collections for each week. For the determination of the total solids, a portion was evaporated to constant weight over a steam bath. Ninety-five per cent solution of alcohol was added from time to time to facilitate dehydration. The water content was estimated by the difference in weight before and after dehydration. Determinations of the nitrogen were carried out by the macro-Kjeldahl method. Determinations of the fat were made for only four patients. The total ether-soluble

34. Rupp, A., and Schlutz, F. W.: Motility of the Empty Stomach in Normal and in Malnourished Asthenic Children, Am. J. Dis. Child. **39**:241 (Feb.) 1930. Hoelzel, F., and Kleitman, N.: Some Conditions Affecting Subjective and Objective Manifestations of Hunger, Arch. Int. Med. **39**:710 (May) 1927.

35. DuBois, E. F.[28b] Wang, C. C.; Hawks, J. E., and Kaucher, M.[27] Wang, C. C.; Kern, R., and Kaucher, M.[9d]

36. Childrey, J. H.; Alvarez, W. C., and Mann, F. A.: Digestion Efficiency with Various Foods and Under Various Conditions, Arch. Int. Med. **46**:361 (Sept.) 1930.

matter was estimated as fat. The figures in tables 7, 8 and 9 are the averages of the several weekly observations for each patient, expressed in terms of grams per day.

OBSERVATIONS

Careful records of the fecal output are available for nine patients of the series. These have been described elsewhere.[37] Analyses of the fat were carried out on only four patients of the series. These observations are recorded in table 7.

The average weight of the output was 165 Gm., with a range of from 80 to 247 Gm. per day. The weekly figures, which are not given in tables 7, 8 and 9, show a rather striking uniformity of output in a given person from week to week.

The total solids in the feces averaged 31 Gm. per day. Not only was this figure constant for a given subject from week to week, but

TABLE 7.—*Analysis of Feces*

Patient	Number of Weeks	Total Weight, Gm.	Solids, Gm.	Percentage of Solids	Water, Gm.	Percentage of Water	Nitrogen, Gm.	Percentage of Nitrogen	Fat, Gm.	Percentage of Fat
1	6	133	19	14	114	86	0.99	0.7	....	....
5	6	136	57	42	79	58	0.66	0.4	42.7	31.0
6	6	242	37	15	205	85	2.13	0.9	2.3	0.9
10	4	80	22	28	58	72	0.89	1.1	....	....
14	3	247	28	11	219	89	1.53	0.6	....	....
15	4	182	32	18	150	82	1.30	0.7	8.0	4.4
16	4	122	22	18	100	82	1.17	0.9	0.7	0.5
17	1	107	19	19	88	81	0.94	0.9	....	....
18	7	239	45	19	194	81	2.02	0.8	....	....
Average.....		165	31	20	134	80	1.29	0.8	....	....

there was markedly little deviation from this average in all the subjects.[19] The figure represents 20 per cent of the total weight of the fresh feces. This percentage, however, varies somewhat more than the dry weight, owing to the greater variations in the water content. One patient averaged 89 per cent water for three weeks without having had diarrhea or having taken cathartics. Another patient averaged only 58 per cent water over a period of six weeks. In the majority, however, the percentage of water ranged from 80 to 85.

The nitrogen content of the stools averaged 1.29 Gm. per day. The lowest value—0.66 Gm.—was obtained for the patient whose stools had a high fat content. The high values—2.13 and 2.02 Gm.—were obtained for the two patients on high caloric and relatively high protein diets. Although these high values are somewhat above the normal limits described by DuBois [28b] (1.8 Gm.), the average value closely approximates the average for his series of patients with typhoid. It is of considerable interest to note that the nitrogen constitutes less than 5 per

37. Strang, J. M., and Cox, A. B.[18] Strang, J. M., and Evans, F. A.[1]

cent of solids of the stool. This figure is somewhat lower than the several ratios recorded by Lusk.

The fat content of the feces of three patients who received ordinary mixed diets ranged from 0.7 to 8 Gm. In one patient who ate 274 Gm. of fat (86 per cent of the 3,000 calories) the fecal fat reached 43 Gm. a day, or 16 per cent of the ingested fat.

Although the absolute figures for the composition of the feces are of interest, their significance becomes greatly increased when viewed in relation to the corresponding food intakes. These facts are summarized in table 8.

In the first two columns of table 8 are recorded the average daily weights of the food intake and of the feces, which are 1,926 and 165

TABLE 8.—*Relation of Components of Feces to Various Food Factors*

Patient	Weight of Food, Gm.	Weight of Feces, Gm.	Ratio of Weight of Feces to Weight of Food, Percentage	Food Solids, Gm.	Fecal Solids, Gm.	Ratio of Fecal Solids to Food Solids, Percentage	Food Nitrogen, Gm.	Fecal Nitrogen, Gm.	Ratio of Fecal Nitrogen to Food Nitrogen, Percentage	Total Weight of Intake, Gm.	Ratio of Fecal Nitrogen to Intake, Percentage	Ratio of Fecal Nitrogen to Fecal Solids, Percentage
1	1,557	133	8.5	465	19	4.1	6.85	0.99	14.5	3,345	0.029	5.2
5	1,303	136	10.4	382	57	14.9	9.04	0.66	7.3	2,994	0.022	1.2
6	2,521	242	9.6	841	37	4.4	18.48	2.13	11.5	4,311	0.049	5.7
10	1,791	80	4.5	500	22	4.4	8.93	0.89	10.0	2,408	0.037	4.0
14	2,240	247	11.0	506	28	5.5	11.20	1.53	13.7	3,953	0.038	5.5
15	1,760	182	10.3	521	32	6.1	8.67	1.30	15.0	3,091	0.042	4.1
16	1,728	122	5.6	521	22	4.2	10.00	1.17	11.7	2,771	0.042	5.3
17	1,730	107	6.2	434	19	4.4	12.00	0.94	7.8	2,837	0.033	5.0
18	2,700	239	8.9	776	45	5.8	14.06	2.02	14.4	4,860	0.041	4.5
Average	1,926	165	8.3	549	31	5.8			11.8		0.037	4.5

Gm., respectively. The fecal output, therefore, constitutes 8.3 per cent of the food intake. However, there is a considerable range of individual variation—from 4.5 to 11 per cent. A somewhat different impression of the relation of the fecal output to the food intake is obtained if the relation between the fecal solids and the food solids is determined. From columns 5 and 6 of table 8 it may be noted that the food solids averaged 549 Gm. and the fecal solids, 31 Gm. The fecal solids correspond to 5.8 per cent of the food solids. The significance of this relation is perhaps emphasized by the relatively slight variations in eight patients—from 4.1 to 6.1. The single large deviation occurred in patient 5, who received a very high fat diet and who produced concentrated stools in which 75 per cent of the solid material was fat. If this single value is omitted from the calculations, the average becomes 4.8 ± 0.6 (12 per cent), which is a variation only half as great as that for the ratio of the fecal weight to the weight of the food.

The nitrogen in the stool was 11.8 per cent of the nitrogen intake. The individual variations ranged from 7.3 to 15 per cent, with an average deviation of 2.4 per cent, or 20 per cent. The nitrogen output appears to be influenced to some extent by the total weight of the intake, as shown in column 12. It may be seen that the nitrogen output corresponds to 0.037 ± 0.006 per cent of the total weight of the intake. These data suggest that although the nitrogen in the stools is influenced by the nitrogen intake, it is also affected by the total mass of the intake.

TABLE 9.—*Relation of Fecal Solids to Food Intake*

	Patient	Number of Weeks	Intake of Food, Calories	Food Solids, Gm.	Fecal Solids, Gm.	Ratio of Fecal Solids to Food Solids, Percentage
2,000 Calorie Diets						
	1	2	2,150	358	27	
	Average			358	27	7.5
2,500 Calorie Diets						
	15	1	2,410	384	30	
	17	1	2,570	434	19	
	Average		2,490	409	25	6.1
3,000 Calorie Diets						
	1	4	2,920	400	18	
	5	6	2,980	382	57	
	10	3	3,090	485	21	
	14	3	3,060	506	28	
	16	2	3,030	482	20	
	Average		3,020	469	29	6.2
3,500 Calorie Diets						
	10	1	3,510	545	23	
	15	3	3,520	566	33	
	16	2	3,600	560	24	
	18	1	3,710	603	27	
	Average		3,580	568	27	4.8
4,500 Calorie Diets						
	18	2	4,400	707	40	
	Average		4,400	707	40	5.7
5,000 Calorie Diets						
	6	6	5,090	841	37	
	18	4	5,250	854	44	
	Average		5,170	848	40	4.7

This observation supports the statement of Whitacre and his associates [28d] that a high proportion of bulk in the diet tends to reduce the utilization of nitrogen. If the fecal nitrogen is compared with the fecal solids it is found that the nitrogen constitutes 4.5 per cent of the solids. If the single variant—that shown by patient 5—is omitted, eight subjects averaged 4.9 ± 0.5 per cent. This average deviation of only 10 per cent suggests that although the nitrogen intake and the bulk of the food affect the fecal nitrogen, the relation of the fecal nitrogen to the fecal solids is even more close.[38]

38. Lusk, G.,[6f] p. 60.

The data just given describe the average relations of the food to the feces for the entire periods of observation. An attempt was made to correlate the fecal output with the several levels of food intake. In table 9 the individual dietary periods are subdivided to indicate the number of weeks during which each patient maintained a given level of intake. The figures recorded for the intake are the averages of the several weeks, not necessarily consecutive, at which the level was maintained.

Five persons maintained intakes of 3,000 calories for eighteen weeks. During this period the fecal solids averaged 6.2 per cent of the food solids. For two week periods at levels of 2,000 and 2,500 calories the relations were 6.1 and 7.5 per cent. On the other hand, when the higher ranges of intake were reviewed, it was found that for seven weeks at the 3,500 caloric level the ratio was 4.8 per cent; and for two weeks at the 4,500 caloric level, 5.7 per cent and, particularly, for ten weeks at the 5,000 caloric level, 4.7 per cent. If these ratios are compared with the average for the entire group for all the periods—5.8 per cent—it will be noted that, contrary to the usual presumption, the ratios are definitely smaller at the higher levels of intake and definitely larger at the lower levels of intake. Such data supply no grounds for the assumption that large food intakes are inadequately handled by the body.

SUMMARY

The importance of a detailed consideration of the relation of the food intake to the fecal output lies in the information relative to the digestion and absorption of food. It is recognized that the feces consist of substances other than the mere residue of ingested food. Nevertheless, these observations provide the only measure at present available for the estimation of the efficiency of digestion. If only a portion of the feces represents the result of failure of digestion and absorption, any conclusion reached by the use of the total values observed will be understatement rather than overstatement of the efficiency of digestion. From the figures relating to the total weights of the food and feces it may be considered that our patients digested and absorbed 92 per cent of the food provided. These figures are similar to the generally accepted values for absorption when calculated in this way. If, however, the relation of the food solids to the fecal solids is considered as the index of absorption, the absorption for eight patients averaged 95 per cent, whereas the single patient with the high fat diet absorbed only 85 per cent of his intake. These figures for the average absorption of a general mixed high caloric diet are well within the recognized limits for ordinary diets. If, carrying the analysis one step further, a comparison is made of the digestive efficiency at the several levels, it may be seen that whereas the average absorption for all levels was 94 per

cent, the higher intakes were more efficiently handled and the lower intakes less efficiently handled than in the average person. It may, therefore, be stated that these studies supply no evidence that the gastrointestinal tracts of thin persons are in any way inferior to those of more robust persons; nor is there any indication of an unusual loss of energy by this route. Rather it is suggested that the digestive and absorptive capacity of a person are adequate for any food intake which he can be induced to ingest.

GENERAL CONCLUSIONS

Studies of the basal metabolism, nitrogen metabolism and efficiency of digestion of patients with severe degrees of undernutrition showed no abnormalities in these factors which could cause the initiation or persistence of such states of undernourishment.

The changes in these three factors which were observed as a result of either the high caloric intake or the increases in weight dependent thereon indicated no new principles of metabolism which might militate against the successful treatment of undernutrition by dietary measures.

FAT TOLERANCE IN HYPERTHYROIDISM

OPAL E. HEPLER, PH.D.
CHICAGO

Hyperthyroidism is accompanied by an increased metabolism which causes the body to burn up first its available carbohydrates, then its superfluous fat and later its protein. The exact source of the energy that goes into the production of the excess heat is obscure. Carbohydrates are, in normal persons, an important source of heat production. In hyperthyroidism the glycogen content of the liver is greatly depleted, if not completely exhausted, as was shown by Cramer and Krause,[1] Kuriyama,[2] Fukui [3] and Coggeshall and Greene.[4] Yet in this condition Denis, Aub and Minot,[5] Gardiner-Hill, Brett and Smith [6] and Sanger and Hun [7] observed reduced tolerance for sugar. Boothby and Sandiford,[8] as a result of extensive experiments, concluded that "there is no measurable increase in the endogenous protein metabolism in exophthalmic goiter; therefore it can not be the cause of the increased basal metabolism in this disease."

Although the oxidation of fat produces the largest amount of heat in the normal person, little attention appears to have been paid to this source of energy in hyperthyroidism. However, it has been assumed that the gradual loss of fat which results from the administration of thyroxin or of thyroid extract is caused to a large extent by the generally greater expenditure of energy and particularly by the increased muscular movement. But Abelin and Kürsteiner [9] brought forward evidence that the thyroid secretion may also exercise a direct

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From the Department of Pathology of Northwestern University Medical School.

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2. Kuriyama, S.: J. Biol. Chem. **33**:193, 1918.

3. Fukui, T.: Arch. f. d. ges. Physiol. **210**:410, 1925.

4. Coggeshall, H. C., and Greene, J. A.: Am. J. Physiol. **105**:103, 1933.

5. Denis, W.; Aub, J. C., and Minot, A. S.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. **20**:964 (Dec.) 1917.

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7. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

8. Boothby, W. M., and Sandiford, I.: Total and Nitrogenous Metabolism in Exophthalmic Goiter, J. A. M. A. **81**:795 (Sept. 8) 1923.

9. Abelin, I., and Kürsteiner, P.: Biochem. Ztschr. **198**:19, 1928.

effect on fat metabolism, since they observed that large doses of thyroid extract cause the disappearance of a considerable proportion of the body fat of rats within from twenty-four to seventy-two hours, that is, before the general metabolic effect of the hormone was detectable. Kommerall [10] produced an increase of 30.5 per cent in the basal metabolism of dogs by feeding dried thyroid; 31.3 per cent of this increase was due to increased protein metabolism, while 68.7 per cent was due to increased fat metabolism.

Most investigators have reported a decrease in the fat content of the blood in hyperthyroidism. Raab [11] stated that the subcutaneous administration of thyreoiodine to dogs in no way influences the fat content of the blood. Sakurai [12] found that a single dose of thyroid emulsion decreased the fatty acid and cholesterol values of the blood of rabbits, while repeated injections increased the values. Thyroidectomy was followed by an increase in the blood fats, which could be prevented temporarily by the injection of thyroid emulsion. Silberstein, Gottdenker and Geiger [13] obtained hypolipemia in cats after the administration of olive oil with as many as six subcutaneous injections of thyreotropic hormone. More than six injections, however, caused hyperlipemia.

Bing and Heckscher [14] obtained low values for the ether-soluble substances of the blood in patients with exophthalmic goiter. The response to 1 Gm. of cream per kilogram of body weight was the same as in normal controls except that the increase of blood fat terminated in from three to four hours in the patients with thyroid disturbance while in the normal controls it continued five hours or more. As the symptoms decreased and after thyroidectomy, the fat and cholesterol content increased. These authors also found in later work [15] that the fat and cholesterol content of the blood in three myxedematous patients was increased and when thyreoiodine was administered it decreased. Clinical hyperthyroidism produced by overdoses of thyreoiodine caused the blood fat and cholesterol values to fall far below the normal concentration. Heckscher [16] observed high blood fat values in adult cretins. In young cretins the values were about normal, but the increase four or six hours after a fat meal was considerably greater than in normal subjects of the same age.

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10. Kommerall, B.: Biochem. Ztschr. **208**:112, 1929.
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13. Silberstein, F.; Gottdenker, F., and Geiger, G.: Klin. Wchnschr. **12**:1225, 1933.
14. Bing, H. I., and Heckscher, H.: Biochem. Ztschr. **158**:403, 1925.
15. Bing, H. I., and Heckscher, H.: Biochem. Ztschr. **162**:32, 1925.
16. Heckscher, H.: Biochem. Ztschr. **158**:422, 1925.

Nicholls and Perlzweig [17] reported a decrease of fatty acids and cholesterol in the plasma of untreated patients with hyperthyroidism, with an increase after treatment with iodine and operation. Parhon and Ornstein [18] stated that intramuscular injections of thyroxin caused a decrease in the cholesterol and fatty acids in five patients.

Kugelmann [19] determined the fat content of the blood during nineteen hours after a carbohydrate-free, fat-rich evening meal in healthy persons and found an increase during the night but a definite decrease by midday. In thyrotoxic patients there was an increase up to midday. Alpern, Tutkewitsch and Besuglow,[20] Leites [21] and Tsuda [22] found that subcutaneous injections of thyroxin in dogs decreased the alimentary blood lipid content after feeding of fat. Leites and Tsuda observed more marked results in male than in female dogs. Parhon and Ornstein [23] noted an increase in the fatty acids and cholesterol of the blood after thyroparathyroidectomy in eight of ten dogs.

Heckscher [24] removed the thyroid gland from a healthy horse and subsequently found an increase in the fat and cholesterol content of the blood. If fat was added to the diet the increase was greater in the thyroidectomized horse than in the normal animal. Nokazawa [25] reported that large doses of thyroid extract reduced the fat content of the whole blood of mice.

More observations have been made on the blood cholesterol in thyroid disease than on the fatty acids. Epstein and Lande,[26] C. J. and M. Parhon,[27] Mason, Hunt and Hurxthal [28] and Hurxthal [29] obtained diminished cholesterol values in patients with exophthalmic goiter. Improvement in the condition due to medical or surgical treatment resulted in a rise in the blood cholesterol to normal levels. These authors, as well as

17. Nicholls, E. G., and Perlzweig, W. A.: J. Clin. Investigation **5**:195, 1928.
18. Parhon, C. I., and Ornstein, I.: Compt. rend. Soc. de biol. **108**:303, 1931.
19. Kugelmann, B.: Ztschr. f. klin. Med. **115**:454, 1931.
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21. Leites, S.: Biochem. Ztschr. **221**:101, 1930.
22. Tsuda, M.: Okayama-Igakkai-Zasshi **44**:605, 1932.
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26. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: I. The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**: 563 (Nov.) 1922.
27. Parhon, C. J., and Parhon, M.: Compt. rend. Soc. de biol. **90**:150, 1924.
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29. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, Arch. Int. Med. **52**:86 (July) 1933.

Luden,[30] Gardner and Gainsborough,[31] Laroche,[32] Hillmann[33] and Bronstein[34] found a marked increase in the blood cholesterol in patients with myxedema; when thyroid treatment was administered the content was reduced. Epstein and Lande[26] concluded that a definite inverse relationship exists between the cholesterol value and the basal metabolic rate. Castex and Schteingart[35] and Bonilla and Moya,[36] on the contrary, could find no relation between the basal metabolic rate and the blood cholesterol value. They concluded that any hypocholesteremia or hypercholesteremia observed in patients with thyroid disease depends not on these conditions but on concomitant causes. Denis,[37] Gechman[38] and Laroche[32] obtained low cholesterol values in extreme cases of hyperthyroidism, while in less serious cases they found normal values. On the other hand, Luden[30] stated that the blood cholesterol in thirty-five cases of exophthalmic goiter was within normal range, even when the basal metabolic rate was 100 per cent above normal. Gardner and Gainsborough[31] and Hinton[39] reported normal cholesterol values in their patients with hyperthyroidism. Hillmann[33] found the blood cholesterol values below normal in five patients with exophthalmic goiter and slightly above normal in six. Rosa and Furtado[40] obtained normal or slightly higher values in nine of eleven patients with hyperthyroidism. Wade[41] observed slightly increased values in thyrotoxic patients before operation. Rothschild and Jacobsohn[42] reported an increase of 20 per cent above the normal values for cholesterol in subjects with experimentally produced thyrotoxic conditions. Macciotta[43] recorded that thyreoiodine increases the serum cholesterol in babies. Pighini and de Paoli[44] observed an increased blood cholesterol during the long administration

30. Luden, G., in Collected Papers of Mayo Clinic, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 470.

31. Gardner, J. A., and Gainsborough, H.: Brit. M. J. **2**:935, 1928.

32. Laroche, G.: Presse méd. **37**:268, 1929.

33. Hillmann, M. L.: Vrach. delo **14**:13, 1931.

34. Bronstein, I. P.: Studies in Cretinism and Hypothyroidism in Childhood: I. Blood Cholesterol, J. A. M. A. **100**:1661 (May 27) 1933.

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37. Denis, W.: J. Biol. Chem. **29**:93, 1917.

38. Gechman, G.: Omsky med. j. **2**:16, 1927.

39. Hinton, J. W.: Am. J. M. Sc. **180**:681, 1930.

40. Rosa, M., and Furtado, D.: Lisboa méd. **6**:493, 1929.

41. Wade, P. A.: Am. J. M. Sc. **177**:790, 1929.

42. Rothschild, F., and Jacobsohn, M.: Ztschr. f. klin. Med. **105**:403, 1927.

43. Macciotta, G.: Zentralbl. f. d. ges. Kinderh. **17**:5, 1925.

44. Pighini, G., and de Paoli, M.: Biochim. e terap. sper. **12**:49, 1925.

of thyroid extract and concluded that cholesterol fixes and neutralizes the thyroid hormone in hyperthyroidism.

M. M. and E. Lévy [45] found that thyroxin reduced the cholesterol values to normal in patients with hypercholesteremia. Christie, Lyall and Anderson [46] observed a great diminution of the blood cholesterol under thyroid therapy in a patient with xanthomatosis with a low basal metabolic rate and hypercholesteremia. Duncan [47] gave thyroid treatment to twenty-two patients with mental disease and obtained a rapid lowering of the serum cholesterol, while Epstein [48] and Liu [49] reduced the hypercholesteremia in nephrosis with thyroid extract. Turner [50] discovered that when thyroid was administered simultaneously with cholesterol it prevented the atheromatous changes usually produced by the administration of this lipoid to rabbits. Goldzieher and Hirschhorn [51] asserted that thyroid residue administered to animals at the same time that an emulsion of cholesterol is injected intraperitoneally prevents the normal storage of cholesterol in the Kupffer cells of the liver.

Parhon and H. and M. Dérevici,[52] Trifon [53] and Blinoff [54] demonstrated that dogs with hyperthyroidism had blood cholesterol values lower than those of normal dogs. However, Clevers [55] observed an increase in the serum cholesterol in dogs with hyperthyroidism. Leupold and Seisser [56] and Kusaka [57] found a decrease of the blood cholesterol in rabbits with hyperthyroidism. Leupold [58] stated that small doses of thyreoiodine decreased the cholesterol content of the blood in rabbits

45. Lévy, M. M., and Lévy, E.: Presse méd. **40**:240, 1932.

46. Christie, J. F.; Lyall, A., and Anderson, T. E.: Brit. J. Dermat. **42**:429, 1930.

47. Duncan, A. G.: J. Ment. Sc. **77**:332, 1931.

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50. Turner, K. B.: J. Exper. Med. **58**:115, 1933.

51. Goldzieher, M. A., and Hirschhorn, L.: The Reticulo-Endothelial System: III. The Influence of Hormones, Arch. Path. **4**:958 (Dec.) 1927.

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53. Trifon, N.: Compt. rend. Soc. de biol. **101**:233, 1929.

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57. Kusaka, S.: Jap. J. Gastroenterol. **4**:139, 1932; abstr., J. A. M. A. **100**: 299 (Jan. 28) 1933.

58. Leupold, E.: Centralbl. f. allg. Path. u. path. Anat. **33**:8, 1923.

while large doses increased it. Rémond, Colombiès and Bernardbeig,[59] Kunde,[60] Werner,[61] Onizawa,[62] Yoshimura,[63] Kunde, Green and Burns [64] and Westra and Kunde [65] noted in thyroidectomized rabbits high cholesterol values, which were reduced by the administration of thyroid. However, Turner and Khayat [66] claimed that thyroidectomy in itself does not cause a rise in the blood cholesterol of rabbits.

From the foregoing review of the literature the following facts are evident: First, little has been done on the problem of fat metabolism in hyperthyroidism; second, conflicting results have been obtained by different workers, some of which are probably due to the use of different methods and others to the use of a single injection of thyroxin, with the tests made immediately or of several injections, with the tests made one or two days later; third, of the few investigators who studied the fat content of the blood in relation to thyroid disease, the majority observed hyperlipemia in hypothyroidism and hypolipemia in hyperthyroidism; fourth, the majority of investigators observed hypercholesteremia in hypothyroidism and a normal or diminished cholesterol content of the blood in hyperthyroidism, and fifth, there seems to be no difference in the results in different species of animals.

METHODS

These experiments were an attempt to determine the effect of hyperthyroidism on fat metabolism. Twenty-two adult dogs were used; four died of acute thyrotoxicosis, and the observations on three others were discontinued because of infections. Complete results were obtained for fifteen animals. Thyrotoxicosis was produced by feeding 10 Gm. of desiccated thyroid daily with the food. Within a week after the feeding of thyroid was begun the dogs began to show loss of weight, great excitability and diarrhea.

Tests for fat tolerance were made on each dog every two or three weeks throughout the experiment until it died. From two to three tests were made before the animal was fed thyroid; these served as controls. The dogs were fed thyroid for different lengths of time, varying from two to three months according to the reaction to it. Then the feeding of thyroid was stopped for from six weeks to two months. This alternation was kept up until the dog died.

The following procedure was used in the fat tolerance tests: After the dog had been starved for four days, 15 cc. of blood was withdrawn from a vein; 10 cc. was placed in a centrifuge tube containing 4 drops of a saturated solution of sodium oxalate, and 5 cc. was placed in another tube containing 2 drops of the oxalate

59. Rémond, A.: Colombiès, H., and Bernardbeig, J.: Compt. rend. Soc. de biol. **91**:445, 1924.

60. Kunde, M. M.: Am. J. Physiol. **76**:225, 1926.

61. Werner, G.: Compt. rend. Soc. de biol. **100**:928, 1929.

62. Onizawa, J.: J. Biochem. **10**:425, 1929.

63. Yoshimura, O.: J. Chosen M. A. **21**:1079, 1931.

64. Kunde, M. M.; Green, M. F., and Burns, G.: Am. J. Physiol. **99**:469, 1932.

65. Westra, J. J., and Kunde, M. M.: Am. J. Physiol. **103**:1, 1933.

66. Turner, K. B., and Khayat, G. B.: J. Exper. Med. **58**:127, 1933.

solution to be used for other chemical tests. The dog was fed 2 cc. of olive oil per pound (0.45 Kg.) of body weight. At one, three, five and seven hour intervals thereafter 15 cc. of blood was withdrawn. The total fatty acid and cholesterol content of the plasma in each of the five samples was determined by Bloor's [67] oxidation method.

In order to determine the amount of fat lost in the stools, the fat in the feces of four dogs was determined at the same time that the fat tolerance tests were made. Two specimens were obtained, one during the starvation period before olive oil was given; the other was the first specimen after the administration of the olive oil. The total fat was estimated by Saxon's [68] method, and duplicate tests were made on each sample.

All the glassware used in the tests was free from fat. In all, there were 2,928 determinations: 1,400 titrations of fatty acids, 238 of which were controls, 1,400 colorimetric determinations of cholesterol, 238 of which were standards, and 128 determinations of fat in the feces.

RESULTS OF EXPERIMENTS

Normal Initial Blood Lipoid Values.—The twenty-two animals showed a marked individual difference in the fat content of the blood at the beginning of the experiment. There seemed to be no similarity in the initial value for blood fat, that is, in the sample taken just prior to feeding the oil, for any one sex or species. The average normal initial value for fatty acids was 313.3 mg. per hundred cubic centimeters, with a range from the minimum of 189 mg. to a maximum of 654. In any one dog the maximum difference among the several values was 157 mg., and the minimum difference, zero, with an average of 62 mg. The average normal initial cholesterol value was 128.9 mg. per hundred cubic centimeters, with a range from a minimum of 76 mg. to a maximum of 202 mg. In any one dog the maximum difference was 51 mg., and the minimum, zero, with an average of 17.6 mg.

However, because of death from infections or acute thyrotoxicosis it was possible to obtain complete results for only fifteen dogs after the feeding of desiccated thyroid. The average normal initial blood fat content of the fifteen dogs varied only slightly from that of the twenty-two dogs, the initial fatty acid content averaging 315.2 mg. per hundred cubic centimeters and the cholesterol value averaging 126 mg.

Initial Blood Lipoid Values During First Period of Feeding of Thyroid.—After two or three weeks of feeding of thyroid the average initial fatty acid content for the fifteen dogs was 300 mg. per hundred cubic centimeters. This was 15.2 mg. lower than the normal average for the same dogs. The animals can be divided into three groups: The first consists of six dogs in which the initial fatty acid content was from 26 to 176 mg. lower than the lowest corresponding normal value.

67. Bloor, W. R.: J. Biol. Chem. **77**:53, 1928.
68. Saxon, G. J.: J. Biol. Chem. **17**:99, 1914.

The average for these dogs after feeding of thyroid was 238.7 mg., which was 95.3 mg. lower than the average (334 mg.) of the lowest normal values for these six dogs. The second group consisted of one dog in which the initial fatty acid content was lower than its corresponding high normal value. The amount after feeding of thyroid was 396 mg., which was 44 mg. lower than the highest normal value. The third group consisted of eight dogs in which the initial fatty acid value was from 5 to 93 mg. higher than the highest corresponding normal value. The average after feeding of thyroid was 333.9 mg., which was 29.5 mg. higher than the average (304.4 mg.) of the highest normal values for the eight dogs.

The average initial cholesterol value after feeding of thyroid was 115.3 mg. per hundred cubic centimeters which was 15.7 mg. lower than the normal average value. The dogs can again be divided into three groups. The first consists of eight dogs in which the initial cholesterol value was from 1 to 74 mg. lower than the lowest corresponding normal value in the group. The average for these dogs after feeding of thyroid was 104 mg., which was 27 mg. lower than the average (131 mg.) of the lowest normal values for the eight dogs. The second group consisted of three dogs in which the initial cholesterol value was lower than the corresponding high normal value. The average after feeding of thyroid was 121 mg., which was 28 mg. lower than the average (149 mg.) of the highest normal values for the three dogs. The third group consisted of four dogs in which the initial cholesterol value was from 2 to 38 mg. higher than the highest corresponding normal value. The average after feeding of thyroid was 132.5 mg., which was 16.5 mg. higher than the average (116 mg.) for the highest normal value for the four dogs.

As feeding of thyroid continued the initial fatty acid content in all but four dogs increased, reaching the maximum from six to nine weeks after the feeding of thyroid was begun. The maximum increase was 372 mg. at eight weeks in dog 8. The minimum increase was 7 mg. at five weeks. In three dogs in which there was a decrease the first initial blood fat value for each dog after feeding of thyroid was higher than the normal value for that dog. This increase made the average initial fatty acid content for all the tests on the fifteen dogs during the entire period of feeding of thyroid 10.9 mg. higher than the normal average.

As feeding of thyroid continued the initial cholesterol value in all the dogs increased, the range being from 2 to 87 mg. However, this increase was not as great in comparison to the increase in fatty acids, as shown by the average cholesterol value for the fifteen dogs, which was exactly the same as the average for the normal dogs.

Initial Blood Lipoid Values After First Period of Feeding of Thyroid.—Eight dogs survived a period of feeding of thyroid of from two

to fourteen weeks; then feeding of thyroid was discontinued for a period of from three to eight weeks. During the rest period the blood fat showed a great increase. The initial fatty acid value increased in the first test in seven of the eight dogs, the range of increase being from 6 to 258 mg., with an average of 119.7 mg. The one dog (dog 12) that did not show an increase had been fed thyroid for only two weeks and probably had not become as thyrotoxic as the others, which had been fed thyroid for at least six weeks. Those which had been fed thyroid for from nine to eleven weeks showed the greatest increase. In only two dogs (except dog 12) was the initial fatty acid value after discontinuation of feeding of thyroid lower than the highest value during feeding of thyroid. The average initial fatty acid value was 446.3 mg., which was 120.2 mg. higher than the average during feeding of thyroid and 131.1 mg. higher than the normal average before feeding of thyroid.

The cholesterol was greatly increased in all the dogs throughout this period. The increase in the initial cholesterol content varied from 10 to 175 mg., and at no time was the cholesterol value as low as the highest value during the previous period. The average initial cholesterol value was 206.9 mg., which was 80.9 mg. higher than the average value during feeding of thyroid and the normal average before feeding of thyroid.

Initial Blood Lipoid Values During Second Period of Feeding of Thyroid.—Six dogs were again fed thyroid after the rest period. All these showed a decrease of from 16 to 90 mg. in the initial fatty acids determined by the first test, which was a much greater decrease than in the first period of feeding of thyroid. The average for the first tests was 332.5 mg., which was 93.5 mg. lower than the average for the rest period for these six dogs. All the initial fatty acid values except one were lower than the lowest value in the preceding period. The average was 366.8 mg., which was 79.5 mg. lower than the average for the previous period.

The initial cholesterol also showed a decrease, the values for the first test ranging from 7 to 136 mg. lower than the values in the last test of the previous period. The cholesterol did not show as great a decrease throughout the second period of feeding of thyroid as did the fatty acids. The average initial cholesterol value was 165.9 mg., which was 41 mg. lower than the average of the previous period.

Normal Curve for Blood Lipoids After Feeding of Olive Oil.—As in the initial blood fat values, there seemed to be no regularity in the degree of hyperlipemia produced by feeding of olive oil either in the individual dog or in the sex or species. Although there was no great difference in the initial fat and cholesterol values in the several tests on the same dog under normal conditions, there was a great difference

in the degree of hyperlipemia produced after feeding of olive oil and in the hour in which the highest values were obtained. The lowest percentage of increase over the initial fat value was 1.7 per cent, and the highest, 102.63 per cent. The average increase in values for all the tests under normal conditions was 52.06 per cent. The greatest individual difference was 92.02 per cent. The height of the curve was reached at five hours in the largest number of tests on the twenty-two dogs, as demonstrated in table 2. However, in table 4 it is

TABLE 1.—*Average Curve for Blood Lipoids for Forty-Three Tests on Twenty-Two Normal Dogs*

Olive Oil	Fatty Acids, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Total, Mg. per 100 Cc.
Before	313.3	128.9	442.2
1 hour after	357.6	127.1	484.7
3 hours after	453.0	124.0	577.0
5 hours after	465.6	127.9	593.5
7 hours after	464.6	128.1	592.7

TABLE 2.—*Height of Curve for Blood Lipoids for Forty-Three Tests on Twenty-Two Normal Dogs*

Peak	Number of Tests	Percentage of Tests
1 hour	2	4.65
3 hours	12	27.91
5 hours	17	39.53
7 hours	12	27.91

TABLE 3.—*Average Curve for Blood Lipoids for Thirty-One Tests on Fifteen Normal Dogs*

Olive Oil	Fatty Acids, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Total, Mg. per 100 Cc.
Before	315.2	126.0	441.2
1 hour after	358.8	125.0	483.8
3 hours after	450.0	120.6	570.6
5 hours after	428.0	121.8	549.8
7 hours after	430.1	123.0	553.1

shown that as many values reached the peak at seven hours as at five hours in the fifteen dogs that were later fed desiccated thyroid.

The cholesterol content did not increase with the fatty acid content but remained practically the same throughout the seven hours, as shown in the average figures for forty-three fat tolerance tests made on twenty-two normal dogs (table 1). In tables 3 and 4 are shown the average results of thirty-one fat tolerance tests and the height of the curve for blood lipoids for the fifteen dogs which were later fed desiccated thyroid.

Curve for Blood Lipoids After Feeding of Olive Oil During First Period of Feeding of Thyroid.—There was a greater increase in the curve for blood lipoids after feeding olive oil during the period of feeding of thyroid than under normal conditions. The average percentage of increase in the first test was 59.3 per cent, which was higher than the average for the period. The greatest increase was in a female dog. The lowest percentage of increase over the initial value for fatty acid plus cholesterol was 2.55 per cent, and the highest 170.15 per cent. The greatest individual difference was 166 per cent. The average increase for all the values during feeding of thyroid was 53.38 per cent. This is confirmed in table 5, which shows that the average increase after feeding of thyroid was 37.22 per cent (from 452.1 to

TABLE 4.—*Height of Curve for Blood Lipoids for Thirty-One Tests on Fifteen Normal Dogs*

Peak	Number of Tests	Percentage of Tests
1 hour	2	6.45
3 hours	9	29.03
5 hours	10	32.26
7 hours	10	32.26

TABLE 5.—*Average Curve for Blood Lipoids for Fifteen Dogs During First Period of Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Total, Mg. per 100 Cc.
Before	326.1	126.0	452.1
1 hour after	344.4	121.3	465.7
3 hours after	452.2	127.1	579.3
5 hours after	494.4	126.0	620.4
7 hours after	470.9	127.1	598.0

620.4 mg.), while it was only 29.32 per cent in table 3 (from 441.2 to 570.6 mg.), showing the average for fifteen normal dogs, and 34.21 per cent in table 1 (from 442.2 to 593.5 mg.), showing the normal average for twenty-two dogs. There was a general shift of the height of the curve for blood lipoids to the fifth and seventh hours, with a greater percentage of increase in this period than in either of the normal groups of fifteen and twenty-two dogs. This is demonstrated by comparing tables 2, 4 and 6. For the twenty-two normal dogs, the curves for blood lipoids had their peaks at five or seven hours in 67.44 per cent of the tests (table 2), for the fifteen normal dogs, in 64.52 per cent (table 4). For the fifteen dogs fed thyroid the curves had their peaks at five and seven hours in 81.2 per cent of the tests (table 6). The average cholesterol curve remained practically the same as the normal cholesterol curve.

Curve for Blood Lipoids After Feeding of Olive Oil After First Period of Feeding of Thyroid (First Rest Period).—During the rest period after feeding of thyroid had been discontinued, although the initial values for fatty acids plus cholesterol were greatly increased, the degree of hyperlipemia after the feeding of olive oil was decreased. The lowest percentage of increase over the initial values was 3.83 per cent, and the highest 43.57 per cent, except for a 53.73 per cent increase in dog 12, which had been fed thyroid for only two weeks and did not show an increase in the initial blood fat value. The greatest individual difference was 28.89 per cent. The average increase for all the values was 23.52 per cent. The increase in the curve for blood lipoids in table 7 (from 653.2 to 775.8 mg.) was only 18.76 per cent. The

TABLE 6.—*Height of Curve for Blood Lipoids for Fifteen Dogs During First Period of Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	0	0
3 hours	8	18.8
5 hours	18	43.7
7 hours	15	37.5

TABLE 7.—*Average Curve for Blood Lipoids for Eight Dogs After Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Total, Mg. per 100 Cc.
Before	446.3	206.9	653.2
1 hour after	482.6	197.9	680.5
3 hours after	522.4	198.9	721.3
5 hours after	579.3	196.5	775.8
7 hours after	527.2	189.7	716.9

height of the peak appeared in a greater percentage at five hours (in 62.5 per cent of the tests) and in a much lower percentage at seven hours (in 25 per cent of the tests), as seen in table 8, than in either the normal dogs or those with hyperthyroidism. Although the cholesterol content was greatly increased before feeding of olive oil, it continued to be high throughout the seven hours, but showed a slight decrease—from 206.9 to 189.7 mg. (table 7).

Curve for Blood Lipoids After Feeding of Olive Oil During Second Period of Feeding of Thyroid.—During the second period of feeding of thyroid the increase in the curve for blood lipoids was not as great as during the first period. The lowest percentage of increase was 11.88 per cent, and the highest 89.87 per cent, both of which were in the same dog. Corresponding values in the first period were 2.55 and 170.15 per cent. The average increase for the separate tests was 42.6

per cent (contrasted with 53.33 per cent). The increase in the average curve for blood lipoids in table 9 (from 532.7 to 714.1 mg.) was 34.21 per cent. The height of the curve for blood lipoids again occurred most frequently at five hours, but there was a higher percentage at three hours (31.3 per cent) than at seven hours (6.2 per cent), as shown in table 10. This is the opposite of the findings shown in table 8 for the rest period. The cholesterol content remained practically the same

TABLE 8.—*Height of Curve for Blood Lipoids for Eight Dogs After Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	2	12.5
3 hours	0	0
5 hours	10	62.5
7 hours	4	25.0

TABLE 9.—*Average Curve for Blood Lipoids for Six Dogs During Second Period of Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Total, Mg. per 100 Cc.
Before	366.8	165.9	532.7
1 hour after	396.5	159.9	556.4
3 hours after	546.5	159.3	705.8
5 hours after	554.1	160.0	714.1
7 hours after	452.2	157.1	609.3

TABLE 10.—*Height of Curve for Blood Lipoid for Six Dogs During Second Period of Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	0	0
3 hours	5	31.3
5 hours	10	62.5
7 hours	1	6.2

as the initial amount throughout the seven hours, that is, lower than that in the previous period.

Fat Content of Feces.—The normal percentage of increase in the fat content of the feces after feeding olive oil was high. In eight tests on the four dogs in which complete results were obtained the average increase was 314.91 per cent over the fat content before olive oil was given. In only one test was the increase less than 100 per cent. During the first period of feeding of thyroid there was a great decrease in the percentage of increase, especially in the first test after

the beginning of the feeding. The average increase during feeding of thyroid was 187.22 per cent. For only one dog (dog 27) were any of the values higher than those obtained under normal conditions. If the two extremely high values for this animal were left out of the calculation for the period of feeding of thyroid the average increase would be only 90.13 per cent. In the three dogs for which feeding of thyroid was discontinued the first values showed a percentage of increase of 194, while the first values during feeding of thyroid showed a percentage of increase of 88. The average increase during the rest period was 152.32 per cent. The feces of only one dog were examined further; during the second period of feeding of thyroid there was an average increase of 43.06 per cent for three tests.

SUMMARY OF RESULTS

There appears to be no regularity in the initial fatty acid or cholesterol content of the blood in different dogs of either sex or of any species.

The type of curve for blood lipoids varied in the individual dog at different times and in the two sexes and the various species.

The initial fatty acid value determined by the first test after feeding of thyroid was slightly lower than the normal value for the individual dogs.

If feeding of thyroid was continued for from six to nine weeks the initial fatty acid content increased.

The cholesterol value remained practically the same as the normal value throughout the period of feeding of thyroid.

The percentage of increase in the curve for blood lipoids after feeding olive oil was greater during the period of feeding of thyroid than in the normal curve.

During the rest period after feeding of thyroid the initial fatty acids and the cholesterol increased greatly.

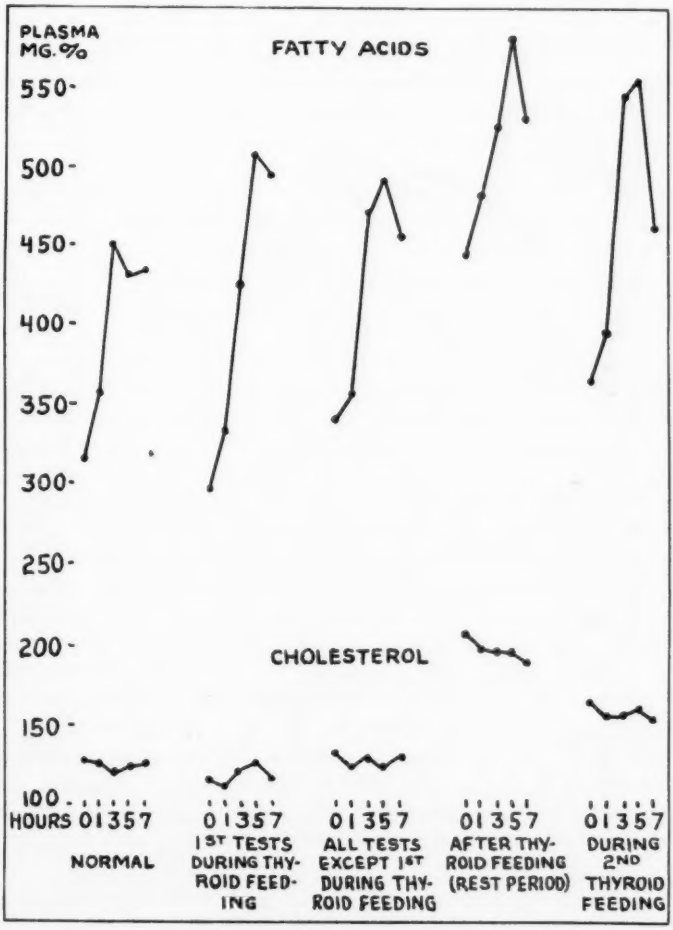
The percentage of increase in the curve for blood lipoids during the rest period was lower than that in the normal period.

During the second period of feeding of thyroid the initial fatty acid and cholesterol values showed a much greater decrease than during the first period of feeding of thyroid.

The percentage of increase in the curve for blood lipoids was greater during the second period of feeding of thyroid than in the rest period, but not as great as during the first period of feeding of thyroid.

During the periods of feeding of thyroid the percentage of increase in the fat content of the feces after feeding olive oil was much less than the normal percentage of increase.

In a preliminary report on seven dogs of this series, Simonds and I [69] concluded that the total lipoid content of the blood plasma is lowered in experimental hyperthyroidism. A more careful analysis



Average curves for blood lipoids in tests for fat tolerance in hyperthyroidism.

of a larger number of determinations on fifteen dogs compelled me to modify that opinion to the extent indicated in the summary.

69. Simonds, J. P., and Hepler, O. E.: Fat Tolerance in Experimental Hyperthyroidism, J. A. M. A. **98**:283 (Jan. 23) 1932.

The foregoing results are demonstrated in the chart, which shows the average fatty acid and cholesterol curves for fifteen dogs during the various periods of these experiments.

COMMENT

After the ingestion of fat there is a continuous absorption of this substance from the intestines into the blood stream and a concomitant continuous passage of fat from the blood into the tissues. The curve for blood lipoids determined by the fat tolerance test represents the difference in the rates of these two processes, that is, the absorption of fat and its utilization or storage. A careful study of the literature failed to reveal any evidence that increased digestion of fat or more rapid absorption of it through the intestinal mucosa can be the cause of the increased blood fat in hyperthyroidism.

Two possible explanations of the hyperlipemia observed in my thyrotoxic dogs present themselves: First, feeding of thyroid has a direct action on the cells of the tissues. That this effect is progressive was demonstrated by Robles.[70] After feeding mice dried thyroid daily he found that tissue respiration was not increased in five days, was slightly increased in ten days and was increased in fifteen days from 20 to 30 per cent. The initial values for blood fat in my dogs were normal or slightly lower than normal during the period of from seventeen to thirty days after the beginning of feeding of thyroid. At this stage of thyrotoxicosis the cells were still capable of utilizing fat, although the slight decrease in the blood fat does not seem comparable to the increased consumption of oxygen of the cells. However, the breakdown of the reserve fat still available would normally cause an increase in the amount of blood fat and might explain the fact that the observed decrease associated with the increasing metabolism was not greater than it was found to be. As feeding of thyroid was continued the increasing toxic effect on the cells decreased their ability to utilize and store fat and thus increased the amount of fat in the blood. This explanation is not satisfactory, because seriously injured cells could hardly be expected to maintain the greatly increased metabolism in hyperthyroidism.

A second explanation may be that as the entire metabolism in hyperthyroidism is established at a higher level than normal so also is the sugar and fat content of the blood established and maintained at a higher level in order to sustain adequately the increased metabolism. Liebermeister[71] in 1875 expressed the view that in fever the

70. Robles, E.: Frankfurt. Ztschr. f. Path. **41**:193, 1931.

71. Liebermeister, C.: Handbuch der Pathologie und Therapie des Fiebers, Leipzig, F. C. W. Vogel, 1875, p. 359.

heat regulating mechanism is adjusted to a higher temperature level. The metabolism in hyperthyroidism is comparable to that in fever in that there are in both an increase in the blood sugar, a decrease in the glycogen of the liver and an increase in the general metabolism. Raab,[72] in 1929, described an increase in the blood fat in experimental fever in dogs but reported [73] in 1933 a decreased curve for blood lipoids after feeding olive oil to patients with fever.

In order to maintain the higher level of metabolism in hyperthyroidism the body must keep a greater amount of fuel in the blood for rapid utilization. While the animal is reaching the height of thyrotoxicosis the blood fat may be normal or slightly decreased because its necessary adjustment to a new and higher level does not keep pace with the metabolism. As the metabolism becomes established at a higher level, an increased amount of fat and sugar must be maintained in the blood in order to sustain the increased metabolism and to meet any emergency. This may be a protective mechanism. Hyperglycemia has been frequently observed in hyperthyroidism.

After feeding of thyroid is discontinued the stimulus of the increased metabolism is withdrawn. The thyroid glands of animals dying at the height of experimental thyrotoxicosis were found to be markedly atrophic. Hence in this condition the natural stimulus to metabolism is lacking, and a state of hypothyroidism exists. The decreased utilization of fat due to the decreased metabolism in hypothyroidism accounts for the great increase of the blood fat after the removal of the stimulus of feeding of thyroid. The body does not adjust itself so rapidly to this change. But after from six to eight weeks the blood fat decreased, showing that by that time either the body had adapted itself to a lower level of metabolism or the thyroid had again assumed its normal function.

The decrease in the initial fat and cholesterol values and in the blood lipoid content after feeding olive oil was more marked during the second period of feeding of thyroid than during the first. In explanation of this it is suggested that because of the increased metabolism after a period in which the metabolism was less than normal there were a greater burning up of fat by the cells and a greater storage of fat. Abelin and Vuille [74] reported that animals become resistant to a second administration of thyroid extract after a two months' rest, as indicated by the ability of the liver to store glycogen. Oberdisse [75] confirmed this by finding that there was not as great an

72. Raab, W.: Wien. Arch. f. inn. Med. **18**:387, 1929.
73. Raab, W.: Ztschr. f. d ges. exper. Med. **89**:616, 1933.
74. Abelin, I., and Vuille, R.: Endokrinologie **2**:248, 1928.
75. Oberdisse, K.: Arch. f. exper. Path. u. Pharmakol. **162**:150, 1931.

increase in the metabolic rate during the second period of feeding of thyroid. However, in my dogs, as the second period of feeding of thyroid continued the blood fat gradually increased, showing that the body was again adjusting itself to a higher level of metabolism.

CONCLUSIONS

1. Feeding of thyroid slightly decreased the initial blood fat during the first month, that is, while the height of hyperthyroidism was being reached.

2. Continued feeding of thyroid was accompanied by an increase in the initial blood fat above the normal value.

3. During the first period of feeding of thyroid there was a decrease in the tolerance of the animal for fat, as demonstrated by the increased curve for blood lipoids.

4. The cholesterol values remained within normal limits during the period of feeding of thyroid.

5. During the rest period after the first period of feeding of thyroid, when the animal was in a state of hypothyroidism, the fat and cholesterol values increased.

6. The blood fat and cholesterol decreased during the second period of feeding of thyroid, possibly due in part to a resistance of the animal to a second administration of thyroid.

7. Two explanations for these results are suggested: first, that the thyroid extract injures by its toxic effect the tissue cells, rendering them incapable of maintaining their normal capacity for storing or utilizing fat, and, second, that in hyperthyroidism the metabolism of the body is established at a higher level and that the fuel constituents of the blood—fat and sugar—likewise must be established and maintained at a higher level in order to sustain this increased metabolism. The second explanation is the more satisfactory.

DISSEMINATION OF AMEBIASIS

FRANCIS W. O'CONNOR, M.D., M.R.C.S.
NEW YORK

The methods of infection by Endamoeba histolytica are more easily followed if one bears in mind the life cycle of the parasite. In this, two phases are recognized: that of the trophozoites or free living forms, capable of life only within the human host, and that of the cysts which survive both within and outside the human host. The trophozoites are found in the wall of the large intestine, where in different conditions they cause varying degrees of ulceration. If during this process they invade the tributaries of the portal vein they are carried to the liver, where they may cause hepatitis or abscess. Less commonly, abscess of the lung, of the brain or of other organs may occur. If the trophozoites are passed by rectum in a dysenteric stool they die rapidly in water or on exposure to air, and if conceivably they could be ingested by another person they would be killed by the gastric juice; therefore it should be realized that the disease-causing phase of the parasite is not the one by which infection is conveyed from man to man.

Should conditions in the colon become unsuitable for the trophozoites they tend to become encysted. They multiply so rapidly that they do not achieve their maximum size and they no longer cytolyze tissue or phagocytose débris and red blood cells. The small precystic parasites thus formed become less active than the parent cell and are subsequently motionless. Finally they secrete a transparent substance which forms an enveloping and highly resistant cyst wall. Persons who pass such cysts in formed or semiformed stools are called "carriers." The carrier may never be aware of any symptoms of infection and may be discovered to be a carrier only on routine examination of his stool. On the other hand, he may give a history of dysentery, or he may be a carrier during intervals between attacks of dysentery.

When passed by rectum the parasites within the cysts retain their vitality for a considerable time provided there is a minimum of moisture. They die rapidly on drying or on exposure to excessive heat. The gastric secretions do not affect them; therefore on entering a new host they pass through the stomach unchanged. In the small intestine the wall of the cyst is digested and the enclosed parasites are liberated.

From the Department of Medicine, Presbyterian Hospital, Columbia University.

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They do not invade the mucosa of the small intestine but are carried through the ileocecal valve to the cecum. Following rapid multiplication they become trophozoites in the large intestine. By means of a powerful secretion they cytolyze the cells of the mucosa and thus make their way to the submucosa and the deeper tissues.

If feces containing cysts are deposited on the ground or in open privies the cysts may be ingested by flies which are capable of depositing them unchanged on food. During rain, washings from feces may carry cysts to streams or wells, in which case infection may occur from drinking water. The number of cysts in the droppings of a fly is not large. Similarly, in water contaminated as described the cysts would be widely distributed and would not reach any one person in large numbers. The fact that amebiasis has generally been considered an endemic rather than an epidemic infection may be attributable to these factors. Furthermore, the fact that many persons become carriers without being conscious of symptoms and that in many clinical cases the onset of symptoms is insidious suggest that the original infection of parasites was small, that in the human host there is a tendency to the development of immunity against the parasite and that only when the resistance of the host is lowered do the parasites multiply with sufficient rapidity to produce the graver manifestations of amebiasis.

Observations have shown that there is a higher incidence of amebiasis among persons handling food than among others. This is especially the case when sanitary conditions are primitive, as in rural districts, in the poorer sections of many towns and in armies maintained under field conditions. The reason for this is probably related to the bionomics of the house-fly and other members of the muscid family which do not bite, such as the bluebottle, the greenbottle and flesh-flies which feed on both feces and food. As is well known, these flies congregate in their largest numbers in and about eating places. In adjacent privies or from excreta on the ground they may ingest cysts of E. histolytica, some of which they pass on food. As this is being repeated constantly, the food of the permanently employed is more likely to be infected than is that of the transient guest. During the recent epidemic in Chicago no cases of amebiasis occurred among the guests in several hotels with a high incidence of carriers on the staff. On the other hand, in two other hotels having the same or lower incidence of carriers, amebic dysentery among the guests assumed epidemic dimensions. A study of 68 carriers was made to see whether cysts might be transmitted by the fingers or the finger-nails, but no parasites were found by either direct microscopic or cultural methods. Moreover, Kaplan has shown that in such quantities of feces as might conceivably adhere to the hand the cysts die within from three to five minutes. These facts suggest that the menace of the person who handles

food is in relation to the accessibility of his excrement to flies and other disseminating sources rather than to any contamination of his hands, except in very rare instances. Here again it is clear that the number of cysts that might possibly be conveyed by the hands must be very small, and by such a method of transmission one might expect only an endemic spread of infection with only mild or subacute symptoms exhibited in many of the cases.

Small foci of amebiasis are not infrequently found in the United States, and Craig (1916) in the study of an outbreak among the troops at El Paso, Texas, observed 118 cases of clinical amebiasis in which the method of infection was definitely attributable to flies. There is, however, no authentic record of an epidemic of amebiasis of the magnitude of that in Chicago in 1933, in which 1,122 cases with 51 deaths have been reported. The outbreak was found to have originated mainly in two adjacent hotels.

At the Presbyterian Hospital, from 4 to 8 cases of amebiasis are studied each month. Fifty per cent of the patients are carriers without apparent symptoms; the remaining half have clinical amebiasis. Among the latter, the symptoms vary from simple diarrhea with a loss of weight to an occasional acute attack of amebic dysentery, but the so-called fulminating type of amebic dysentery commonly seen in the tropics is rarely observed. In September 1933, a patient with a severe case of amebic dysentery was admitted, and since that time 20 cases have been studied in the hospital, all the patients having visited Chicago in 1933. In addition, I have studied other cases in Chicago and have seen the autopsy material in 5 fatal cases. Furthermore, through the courtesy of the president of the Chicago Board of Health, I have been able to study the clinical histories in the replies to questionnaires from many other patients. From the various sources some suggestive facts have emerged.

Many persons were exposed to infection for only a few hours. In a large percentage the period between the exposure and the onset of symptoms was very short, averaging from ten to fifteen days. In the majority of victims the onset of acute dysentery was sudden, without previous discomfort or warning. The symptoms were generally more severe than those seen in general practice in this country, and the course of the disease was rapid. The frequency of tenesmus indicated that the rectum was involved in most cases. Complications in the liver, especially abscess, were common and occurred shortly after exposure to the infection. A study of the autopsy material confirmed the clinical histories and observations. In most cases the greater part of the mucous membrane of the colon was destroyed. Typical amebic ulcers were invariably found in the rectum at autopsy and on proctoscopic examination during life. In the 5 autopsies mentioned the liver showed multiple

abscesses, and in 1 case an abscess was also found in the lung. The foregoing observations were made on severe or fulminating types of amebic dysentery, which were in marked contrast to the subacute picture usually seen in this country.

The facts described suggested that in many cases the method of infection could not possibly be explained by the hitherto recognized methods. In Chicago, flies are a minor problem, and there are neither wells nor streams from which drinking water is supplied. Considering all the facts, it seemed reasonable to assume that infection in this epidemic was due to a massive contamination with cysts of E. histolytica of the drinking water of the two hotels in question. This seemed more likely since one hotel derives its water from the main which supplies the other. On such a supposition it is conceivable that the patients ingested large numbers of cysts on one occasion and probably in many instances within a short space of time, before any immunity could be developed in the host. Such a possibility would explain the very rapid onset of symptoms.

In November 1933 a survey by sanitary engineers of the Chicago Board of Health was made of the plumbing of the hotels concerned, and three potential disease hazards were discovered. When many of the toilets were flushed at the same time, as would occur when a hotel is full to capacity with guests, back siphonage from toilets to the water mains was observed. In June 1933, during local storms, water from the street penetrated to the basement of one of the hotels, resulting in the mixture of floor water and feces from an open sewer which submerged the ice plant and other equipment of the hotel. Subsequently cross-connections were found between the sewage pipes and the mains for drinking water. While it has not been definitely decided which of these hazards was particularly responsible for the outbreak, it seems probable that on the evidence available the cross-connections, notoriously the cause of recent epidemics of bacterial disease, will be found to be the responsible agent.

Since there are carriers in all parts of the United States and since definite foci of infection have been reported in some localities, it is possible that in many large cities where hotels possess antiquated plumbing such outbreaks as occurred in Chicago will again occur under conditions of congestion.

The relatively large number of cases of amebiasis encountered each month during routine practice at the Presbyterian Hospital is not considered alarming. The patients come from all over this continent and others and their cases represent mainly sporadic instances of infection; but when even a small "group" of cases presents itself from one locality or when more than one member of a family is found to be infected, the most stringent inquiry should be instituted with a view to preventing a further spread of the infection.

BLOOD

A REVIEW OF THE RECENT LITERATURE

CYRUS C. STURGIS, M.D.

RAPHAEL ISAACS, M.D.

S. MILTON GOLDHAMER, M.D.

FRANK H. BETHELL, M.D.

AND

GEORGE E. FARRAR, M.D.

The Staff of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan

ANN ARBOR, MICH.

To those who have been closely identified with the field of diseases of the blood it is unnecessary to state that during the past decade there has been at least as much progress in the field of hematology as in any other aspect of internal medicine. Important contributions from both a clinical and a scientific standpoint have been made in recent years from almost every country in the world. As a result, a voluminous literature bearing on the subject has accumulated which makes a complete review impossible. We have attempted, therefore, to select only those articles which have the most important bearing on the recent advances in the subject. Doubtless some valuable papers have been unintentionally omitted, and for these omissions we extend our apologies.

Although the primary purpose of this review is to consider the work of the past year in hematology, a number of fundamental articles published prior to this time have been included for the sake of completeness.

PERNICIOUS ANEMIA

ETIOLOGY

Any discussion of the etiology of pernicious anemia would be incomplete if it did not include a résumé of the fundamental work of Castle and his associates which was published in the *American Journal of Medical Sciences* during the years 1929 to 1931.[1] In a series of care-

1. (*a*) Castle, W. B.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748, 1929. (*b*) Castle,

(Footnote continued on next page)

fully performed experiments it was demonstrated that in patients with pernicious anemia there is an inability of the gastric mucosa to secrete an unidentified substance (the intrinsic factor) which interacts with some article of diet to form a material which controls the maturation of the red blood cells in the bone marrow. It was demonstrated that the underlying cause of true addisonian pernicious anemia is a defect in the gastric secretion. The exact nature of the intrinsic factor has not been determined. It is not one of the known components of the gastric juice, such as hydrochloric acid, rennin or pepsin, but it is an organic substance, it is thermolabile, and there is some evidence which indicates that it is possibly an enzyme or an enzyme-like substance.

Strauss and Castle [2] have stated that the extrinsic factor may be defined as a substance closely related to vitamin B_2 if it is not vitamin B_2. They gave a patient with true addisonian pernicious anemia 12 Gm. daily of an autolyzed yeast preparation for ten days without effect. When the same amount of this preparation was administered daily with 150 cc. of normal human gastric juice a characteristic reticulocytic response and an increase in the total red blood cell count resulted. Other observers,[3] using the whites of hens' eggs as a source of vitamin B_2, were unable to influence the regeneration of red blood cells when this substance was given alone or after incubation with gastric juice. Lassen and Lassen [4] gave various yeast preparations alone and after incubation with gastric juice and concluded that the preparations are without any effect or possibly contain minimal amounts of the anti-

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W. B., and Townsend, W. C.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Gastric Juice, ibid. **178**:764, 1929. (*c*) Castle, W. B.; Townsend, Wilmot C., and Heath, Clarke, W.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, ibid. **180**:305, 1930. (*d*) Castle, W. B.; Heath, Clarke, W., and Strauss, M. B.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, ibid. **182**:741, 1931.

2. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, Activation of Yeast Derivatives with Normal Human Gastric Juice, New England J. Med. **207**:55, 1932.

3. Wills, L., and Naish, A.: A Case of Pernicious Anemia Treated with Vitamin B_2 from Egg White, Lancet **2**:1286, 1933.

4. Lassen, H. C., and Lassen, H. K.: Yeast or Vitamin B_2 as "Extrinsic Factor" in Treatment of Pernicious Anemia, Am. J. M. Sc. **188**:461, 1934.

anemia factor. They concluded that the extrinsic factor is not identical with any fraction of the vitamin B complex. It is stated, however, that some kinds of commercial yeast or yeast preparations contain a certain amount of antianemia principle. Wills concluded [5] that one preparation, which is an autolyzed yeast extract, has a curative effect in certain cases of tropical macrocytic anemia. This may be due to the presence of a product which is developed as a result of the autolysis and the breaking down of protein. Ungley and James [6] reported that 10 of 18 patients with addisonian pernicious anemia showed some hematologic response when yeast or wheat germ was administered by mouth. They concluded that "causes other than deficient secretion of the intrinsic factor have contributed to the development of the syndrome." They listed the following possible causes: an inadequate ingestion of the extrinsic factor, a destruction of or an inability to absorb the material which results from the reaction between the intrinsic and extrinsic factors and a failure to store the material in the liver or an increased demand for it, as in pregnancy. They concluded that the extrinsic factor is present in wheat germ and in fresh and autolyzed yeast. There is no parallelism between the amount of vitamin B_2 in yeast and its effect on hematopoiesis in pernicious anemia. Diehl and Kühnau [7] administered a purified vitamin B_2 preparation alone and after incubation with normal gastric juice to patients with pernicious anemia and did not observe a significant hematopoietic effect. Castle [8] recently stated that he is now fully prepared to relinquish the suggestion that vitamin B_2 is the extrinsic factor. Klumpp and Koletsky [9] thoroughly summarized the literature dealing with the relation of gastric secretion to hematopoiesis. Their paper gives a very complete bibliography of the subject.

Isaacs and Goldhamer [10] emphasized that patients with pernicious anemia have a diminished amount of gastric secretion and suggested that this may be of importance from the standpoint of the etiology of the disease. It was found that the average rate of secretion was 20 cc.

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5. Wills, L.: Nature of the Hematopoietic Factor in Marmite, Lancet **1**:1283, 1933.

6. Ungley, C. C., and James, G. V.: Effect of Yeast and Wheat Embryo in Anemias: Nature of Haematopoietic Factor in Yeast Effective in Pernicious Anemia, Quart. J. Med. **3**:523, 1934.

7. Diehl, F., and Kühnau, J.: Ist Vitamin B_2 der therapeutisch wirksame äussere Faktor beim Morbus Biermer? Deutsches Arch. f. klin. Med. **176**:149, 1933.

8. Lassen and Lassen,[4] editor's footnote.

9. Klumpp, T. G., and Koletsky, S.: The Relation of Gastric Secretion to Hematopoiesis, Ann. Int. Med. **8**:991, 1935.

10. Isaacs, R., and Goldhamer, S. M.: Rôle of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **31**:706, 1934.

per hour in a group of patients with pernicious anemia as compared with an average rate of 150 cc. per hour for normal persons. In support of this theory they collected 1,500 cc. of gastric juice from five patients with pernicious anemia. One hundred and fifty cc. of this was incubated with 200 Gm. of meat and was administered to a patient with pernicious anemia daily for ten days. There was a rise of the reticulocyte count and an increase in the hemoglobin content and red blood cell count, which indicated that the gastric secretion of patients with pernicious anemia has some antianemic effect provided it is administered in sufficient quantities. In support of this view it has been determined [11] that there is a direct relationship between the rate of gastric secretion and the level of the red blood cell count in patients with pernicious anemia; that is, the greater the rate of gastric secretion, the higher the red blood cell count.

Recently Morris and his associates [12] reported that the injection intramuscularly, of concentrated gastric juice from a normal person produced a reticulocytic response and a remission in patients with pernicious anemia. It was found that the active principle was heat-labile and was dialyzable through a collodion sac and resisted chemical treatment which was known to destroy enzymes. Fouts, Helmer and Zerfas [13] undertook similar studies and found that when fresh gastric juice from a normal subject was concentrated at icebox temperature by ultrafiltration the material had no antianemic effect when injected intramuscularly into patients with pernicious anemia. When this material, however, was diluted with water and was then concentrated again by vacuum distillation at 40 C. it was found to be potent. Furthermore, when the inactive fresh juice was stored in the icebox for two months and was then concentrated by ultrafiltration it had an active antianemic effect. It is thought that gastric juice becomes potent only after some chemical reaction occurs, and the rate at which this proceeds is directly proportional to the temperature of its environment. It has been concluded by some [13] that both the intrinsic and the extrinsic factors are present in normal gastric juice, which reacts to form the substance which is effective in pernicious anemia. Meulengracht [14] undertook to

11. Goldhamer, S. M.: Relationship Between the Gastric Juice Volume and Erythropoiesis in Patients with Untreated Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **32**:476, 1934.

12. Morris, R. S.; Schiff, L.; Foulger, J. H.; Rich, M. L., and Sherman, J. E.: The Treatment of Pernicious Anemia: Effect of a Single Injection of Concentrated Gastric Juice (Addisin), J. A. M. A. **100**:171 (Jan. 21) 1933.

13. Fouts, P. J.; Helmer, O. M., and Zerfas, L. G.: The Formation of a Hematopoietic Substance in Concentrated Human Gastric Juice, Am. J. M. Sc. **187**:36, 1934.

14. Meulengracht, E.: The Presence of the Anti-Anemic Factor in Preparations of Dried Stomach Substance from the Cardia, Fundus and Pylorus Respectively, Acta med. Scandinav. **82**:352, 1934.

determine whether the potent antianemic substance of hog stomach is present in the fundic, pyloric or cardiac region of the stomach. These three areas were carefully separated in fresh hog stomach, prepared in dried, defatted and pulverized form and administered to patients with pernicious anemia. Material obtained from the fundus was inactive. Meulengracht concluded, therefore, that the active principle is not secreted by the surface epithelial cells, the parietal cells or the chief cells. The material made from the pylorus exhibited a striking activity, and it was suggested that the pyloric glands actually secrete the specific substance. The results obtained from the preparation derived from the cardia were inconclusive. It was suggested that pernicious anemia is due to atrophy and inactivity of the pyloric and possibly of the cardiac gland cells. In studying 151 patients with pernicious anemia at necropsy Brown [15] found gross lesions involving the gastro-intestinal tract in 82. In 41 of the 42 instances in which the gastric tissue was examined microscopically there was chronic gastritis with or without a loss of glandular epithelium. In 37 there was a disappearance of acidophilic cells to which is ascribed the associated achylia gastrica.

A number of investigators [16] have made observations which indicate that the liver is an important organ for the storage of the antianemic factor in human beings. It was shown that the liver of patients with pernicious anemia who were adequately treated contained the antianemic principle and that it was absent from the liver of those who were inadequately treated. The importance of the liver as a storage depot is emphasized by the recent work of Goodman, Geiger and Claiborn,[17] who concluded that after total removal of the stomach in the pig there is a progressive loss of antianemic potency of the liver which becomes apparent as early as the third month. They cited their work as confirming that of Bence.[18]

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15. Brown, Madelaine, R.: The Pathology of the Gastro-Intestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord: A Study of One Hundred and Fifty-One Autopsies, New England J. Med. **210**:473, 1934.

16. Richter, O.; Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," Proc. Soc. Exper. Biol. & Med. **29**:1093, 1932. Wilkinson, J. F., and Klein, L.: The Hemopoietic Activity of Normal and Abnormal Human Liver with Special Reference to Pernicious Anemia, Quart. J. Med. **3**: 341, 1934. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Rôle of the Liver in Hematopoiesis, Am. J. M. Sc. **188**:193, 1934.

17. Goodman, L.; Geiger, A. J., and Claiborn, L. N.: Anti-Anemic Potency of Liver After Gastrectomy in Swine, Proc. Soc. Exper. Biol. & Med. **32**:810, 1935.

18. Bence, J.: Die Rolle des Magens und der Leber in der Pathologie der perniziösen Anämie, Ztschr. f. klin. Med. **126**:127, 1933.

ACHYLIA GASTRICA

The acidity of normal gastric juice was demonstrated in 1780, and the absence of free hydrochloric acid in the gastric juice of patients with pernicious anemia was noted in 1886. The latter observation has been verified by innumerable investigators. With the advent of the fractional method of gastric analysis in 1914 and the demonstration of the value of injections of histamine it was possible to evaluate more accurately the achlorhydric condition and to emphasize further the profound secretory dysfunction in pernicious anemia.

Apparently there are two schools of thought regarding achlorhydria in pernicious anemia. While many writers have stressed the point that the presence of free hydrochloric acid is not compatible with the diagnosis of true pernicious anemia,[19] others have reported exceptional cases of pernicious anemia in which free acid was present in the gastric juice.[20] In the light of the recent developments of the pathologic physiology of macrocytic anemia and the newer methods of gastric analysis the diagnosis in many of these cases may be questioned. Likewise, the reports of the return of free hydrochloric acid in cases of pernicious anemia in induced remission should be more closely investigated, as the general consensus is that there is no return of this function,[21] although there is an increase in the volume of gastric juice and a suggested increase in the amount of intrinsic factor.[22]

Fractional gastric analyses with injections of histamine have revealed several interesting findings. Apparently there is no demonstrable deficiency in salivary amylase in patients with pernicious anemia.[23]

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19. (*a*) Haden, Russell L.: Macrocytosis of the Erythrocytes and Achlorhydria in Pernicious Anemia, J. A. M. A. **98**:202 (Jan. 16) 1932. (*b*) Bockus, H. L.; Bank, J., and Willard, J. H.: Achlorhydria with Review of Two Hundred and Ten Cases in Patients with Gastro-Intestinal Complaints, Am. J. M. Sc. **184**: 185, 1932. (*c*) Hartfall, Stanley, J.: The Secretion of Gastric Juice in Response to Histamine in Addisonian Anaemia, Guy's Hosp. Rep. **83**:37, 1933. (*d*) Simpson Memorial Institute: Unpublished data. (*e*) Wilkinson, John F.: The Gastric Secretion in Pernicious Anemia, Quart. J. Med. **1**:361, 1932.

20. Barnett, C. W.: The Significance of the Gastric Secretions in Pernicious Anemia, Am. J. M. Sc. **182**:170, 1931. Levin, A. L.: The Occurrence of a Pernicious Anemia Syndrome in the Presence of Normal Gastric Acidity, Am. J. Digest. Dis. & Nutrition **1**:240, 1934. Castle, Heath and Strauss.[1d] Wilkinson.[19e]

21. Davidson, L. S. P.: Pernicious Anaemia with Return of Hydrochloric Acid and Ferments After Treatment, Brit. M. J. **1**:182, 1933. Wilkinson.[19e]

22. Goldhamer, S. M.; Isaacs, R., and Sturgis, C.C.: The Quantitative Relationship Between the Amount of the "Intrinsic Factor of Castle" and the Maturation of Red Blood Cells in Patients with Pernicious Anemia, J. Clin. Investigation, to be published.

23. Emerson, C. P. and Helmer, O. M.: A Study of the Salivary Amylase in Patients with Pernicious Anemia, J. Lab. & Clin. Med. **19**:504, 1934.

Both the gastric juice after fasting and the specimens obtained following stimulation with histamine are markedly decreased in volume, and the mucus may be increased, normal or diminished;[24] there is no free hydrochloric acid present, the total acid is decreased[25] and pepsin and rennin are absent or present in negligible amounts;[26] the total chloride content is reduced;[26a] the value for protein nitrogen is increased, and that for nonprotein nitrogen is within normal limits.[27] Injections of histamine, acetylcholine and physostigmine have practically no effect on altering the gastric secretion in patients with pernicious anemia.[28] The duodenal contents reveal the presence of pancreatic enzymes, although the amount may be reduced.[26a] The latter observation has been questioned.[29]

The truth of the preceding findings has been substantiated by an analysis of the tissue obtained from patients with pernicious anemia.[30] An analysis of the gastric mucosa revealed the absence of proteolytic enzymes. The pancreatic specimens contained a normal amount of tryptic, amolytic and proteolytic enzymes. The duodenal tissue contained a sufficient amount of enterokinase. In weighing all the evidence submitted it appears that pernicious anemia is associated with true achylia gastrica.

MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

It is the universal opinion that degeneration of the spinal cord and the brain in cases of pernicious anemia is a part of the disease process. Some authors have reported the occurrence of involvement of the spinal

24. (*a*) Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Gastro-Intestinal Studies; Gastric Juice in Pernicious Anemia, J. Clin. Investigation **11**:1129, 1932. (*b*) Hartfall.[19c] (*c*) Wilkinson.[19e]

25. Helmer, Fouts and Zerfas.[24] Footnote 19.

26. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: (*a*) Gastro-Intestinal Studies: Pancreatic Enzymes in Pernicious Anemia, J. Clin. Investigation **12**: 519, 1933; (*b*) Gastro-Intestinal Studies: The Relation of p_H to the Pepsin and Rennin Content of the Gastric Juice, Am. J. Digest. Dis. & Nutrition **1**:120, 1934. (*c*) Wilkinson.[19e]

27. Burger, G. N.; Hartfall, S. J., and Witts, L. J.: The Secretion of Mucus by the Stomach with Special Reference to Achlorhydric Anaemias, Guy's Hosp. Rep. **83**:497, 1933.

28. Wilkinson, John F.: The Action of Acetylcholine on the Gastric Secretion in Man, Brit. J. Exper. Path. **13**:141, 1932. Burger, Hartfall and Witts.[27] Hartfall.[19c]

29. Cheney, G., and Niemand, F.: A Possible Relationship of Pancreatic Insufficiency to Addison-Biermer (Pernicious) Anemia, Arch. Int. Med. **49**:925 (June) 1932.

30. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Gastro-Intestinal Studies: Determination of Enzymes on Autopsy Specimens from Cases of Pernicious Anemia and Pellagra, Arch. Int. Med. **53**:675 (May) 1934.

cord in 90 per cent or more of their cases,[31] while others have noted it in less than 25 per cent.[32] The majority of investigators, however, are of the opinion that more than 70 per cent of the patients exhibit neurologic manifestations.[33] These figures have been supported by autopsy findings.[34] With the advent of antianemia therapy the incidence of involvement of the central nervous system is increasing.[35]

Although cerebral changes were noted first by Addison in his classic description, their importance has received too little attention. Recently several authors have stressed the frequent occurrence of cerebral changes, noting their presence in over 60 per cent of the patients with pernicious anemia.[36]

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31. (*a*) Ahrens, R. S.: Neurologic Aspects of Primary Anemia, Arch. Neurol. & Psychiat. **28**:92 (July) 1932. (*b*) Smithburn, R. C., and Zerfas, L. G.: The Neural Symptoms and Signs in Pernicious Anemia: Effects of Liver Extract, ibid. **25**:1100 (May) 1931. (*c*) Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

32. Young, Richard H.: Neurologic Features of Pernicious Anemia, J. A. M. A. **99**:612 (Aug. 30) 1932.

33. Baker, B. M., Jr.; Bordley, J., III, and Longcope, W. T.: (*a*) The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, Am. J. M. Sc. **184**:1, 1932. (*b*) The Effect of Liver and Liver Extract upon the Symptoms and Signs Referable to the Nervous System in Pernicious Anemia, Minnesota Med. **13**:815, 1930. (*c*) Grinker, R. R.: Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, Arch. Int. Med. **38**:292 (Sept.) 1926. (*d*) Reese, Hans H., and Beigler, S. K.: Subacute Combined Degeneration of the Spinal Cord and Pernicious Anemia, Am. J. M. Sc. **171**:194, 1926. (*e*) Riley, W. H.: A Clinical Study of Two Hundred and Sixty-Four Cases of Pernicious Anemia with Special Reference to the Involvement of the Central Nervous System, Bull. Battle Creek San. & Hosp. Clin. **18**: 195, 1923. (*f*) Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord; Symptomatology and Effects of Liver Therapy, Brain **52**: 271, 1929.

34. Hadfield, G.: The Central Nervous System in Addisonian Anemia, Bristol Med.-Chir. J. **44**:21, 1927.

35. Kiely, Charles: Neurologic and Psychopathic Manifestations of Pernicious Anemia, J. Michigan M. Soc. **31**:272, 1932. Young.[32]

36. (*a*) Lurie, Louis A.: Pernicious Anemia with Mental Symptoms: Observations on Varying Extent and Probable Duration of Central Nervous System Lesions in Four Necropsied Cases, Arch. Neurol. & Psychiat. **2**: 67 (July) 1919. (*b*) McAlpine, Douglas: A Review of the Nervous and Mental Aspects of Pernicious Anemia, Lancet **2**:643, 1929. (*c*) Piney, A.: Mental Changes Associated with Pernicious Anaemia, J. Neurol. & Psychopath. **13**:127, 1932. (*d*) Skoog, A. L.: Neurologic Manifestations in Pernicious Anemia, J. A. M. A. **87**:1957 (Dec. 11) 1926. (*e*) Smith, Lauren H.: Mental and Neurologic Changes in Pernicious Anemia: Report of Case with Treatment by Minot-Murphy Diet, Arch. Neurol. & Psychiat. **22**:551 (Sept.) 1929. (*f*) Warburg, E. J., and Jorgensen, S.: Psychoses and Neurastheniae Associated with Achylia Gastrica and Megalocytosis and Relation Between This Syndrome and Pernicious Anemia: One Psychosis, Acta med. Scandinav. **69**:537, 1928; Hospitalstid. **71**:974, 1928. (*g*) Footnotes 31, 32 and 33*a*, *b*, *c*, *d*.

The etiology of the changes in the nervous system remains obscure. The old theory of a neurotoxin as the causal factor is supported by many.[37] More recently, as a result of experimental evidence, it is believed that the manifestations in the cord may result from a vitamin deficiency;[38] others maintain that there is a disturbance in lipid metabolism, and still others support the view that the changes are related to the anemia.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bladder.[31c] The character of the signs depends on whether the changes in the posterior or in the lateral columns of the cord predominate. The reflexes may be increased, decreased or lost. The outstanding sign is a disturbance in the vibratory sensation. Any of the cranial nerves may be involved, but this is relatively rare.[31a] Manifestations of cerebral involvement vary from mild irritability to severe mania; they may be present alone or in association with disturbances of the cord, with or without evidence of anemia, and they may present themselves as the earliest and only manifestation of pernicious anemia.

Conclusions drawn from the benefits of therapy must be guarded, as it is known that there may be spontaneous variations in the intensity of the neurologic manifestations without treatment. Many authors have reported distinct improvement with large doses of liver;[39] others have recommended the administration of desiccated stomach, liver extract

37. Camac, C. N. B., and Milne, L. S.: The Spinal Cord Lesions in Two Cases of Pernicious Anemia, Am. J. M. Sc. **140**:563 (Oct.) 1910.

38. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930. Suzman, M. M.; Muller, G. L., and Ungley, C. C.: An Attempt to Produce Spinal Cord Degeneration in Dogs Fed a High Cereal Diet Deficient in Vitamin A: The Incidental Development of a Syndrome of Anemia, Skin Lesions, Anorexia, and Changes in the Concentration of Blood Lipoids, Am. J. Physiol. **101**:529, 1932.

39. (*a*) Davison, Charles: Spinal Cord Changes in Subacute Combined Degeneration Following Liver Therapy: Histopathologic Study, Proc. Soc. Exper. Biol. & Med. **28**:639, 1931. (*b*) Farquharson, Ray F., and Graham, Duncan: Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, Canad. M. A. J. **23**:237, 1930. (*c*) Fried, B. M.: Subacute Combined Degeneration of Spinal Cord in Pernicious Anemia: Treatment with Liver Diet, J. A. M. A. **92**:1260 (April 13) 1929. (*d*) Garvey, P. H.; Levin, P. M., and Guller, E. I.: Effect of Liver Therapy on the Neurologic Aspects of Pernicious Anemia, Ann. Int. Med. **6**:1441, 1933. (*e*) Minot, George R.: The Treatment of Anemia, with Comments on Food Deficiency and Its Relation to the Nervous System, Tr. Am. Neurol. A. **57**:329, 1931. (*f*) Starr, Paul: The Prevention of Spinal Cord Degeneration in Pernicious Anemia (Cases with Progression of Cord Symptoms), J. A. M. A. **96**:1219 (April 11) 1931. (*g*) Suzman, M. M.: Effects of Liver Therapy in One Hundred Cases of Subacute Combined Degeneration of the Cord, Tr. Am. Neurol. A. **57**:339, 1931. (*h*) Footnotes 31*a*, 33*f* and 36*e*.

(orally and parenterally),[40] preparations of iron,[41] vitamins,[42] solution of potassium arsenite and brain substance.[43]

Antianemia therapy, when given in a sufficient amount, does not have a specific curative effect on degeneration of the spinal cord but contributes indirectly to the improvement of the neurologic manifestations. The primary effect is an improvement in the general feeling of well-being of the patient.

In analyzing the results of the various investigators it is apparent that symptomatic improvement occurs in about 50 per cent of the patients, but rarely, if ever, is there any improvement in the signs. Manifestations referable to the posterior columns respond more readily than do those due to lesions of the lateral columns.[44] If the cerebral changes are a result of the disease process, improvement may be anticipated;[45] however, if a psychosis exists independent of pernicious anemia, no improvement can be expected.

TREATMENT

Experience of many workers during the past eight years has confirmed the hematopoietic activity of the following agents in the treatment of pernicious anemia: liver; liver extracts administered by mouth and intramuscularly[46] and intravenously;[47] desiccated, defatted

40. Footnotes 31*b* and 33*a*.

41. Sargant, Will: Treatment of Subacute Combined Degeneration of Cord by Massive Iron Dosage, Lancet **1**:230, 1932. Snowman, L. V.: A Case of Combined Degeneration of the Cord Treated with Massive Dosage of Iron, ibid. **1**:613, 1932.

42. Fouts, P. J.; Kempf, G. F.; Greene, J. A., and Zerfas, L. G.: Vitamin B Intravenously for Treatment of Neurological Changes in Pernicious Anemia, J. Indiana M. A. **25**:448, 1932. Footnote 39*a*.

43. Ungley, Charles C.: Effect of Brain Diet in Pernicious Anemia, Lancet **2**:63, 1931. Effect of Brain Diet in Subacute Combined Degeneration of Cord, ibid. **1**:227, 1932.

44. Footnotes 31*a*, 34 and 39*b*.

45. Tenney, C. F., and Goldstein, Eli: Mental Symptoms of Pernicious Anemia and Their Response to Liver Therapy, M. Clin. North America **17**:185, 1933. Footnotes 31*c* and 36*c* and *e*.

46. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, J. A. M. A. **98**:1620 (May 7) 1932. Conner, H. M.: Injection of Liver Extract in Treatment of Pernicious Anemia, ibid. **99**: 614 (Aug. 20) 1932. McHenry, E. W.; Mills, E. S., and Farquharson, R. F.: Treatment of Pernicious Anemia by the Intramuscular Administration of Liver Extract, Canad. M. A. J. **28**:123, 1933. Murphy, W. P.: The Parenteral Use of Liver Extract in Pernicious Anemia, J. A. M. A. **98**:1051 (March 26) 1932.

47. Isaacs, R.; Sturgis, C. C.; Goldhamer, S. M., and Bethell, F. H.: The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, J. A. M. A. **100**:629 (March 4) 1933. Fouts, Paul J., and Zerfas, L. G.: Use of Liver Extract Intravenously: Report of Ten Cases, Arch. Int. Med. **50**:27, 1932. Freeman, E. T.: Intravenous Liver Therapy in Pernicious Anemia, Irish J. M. Sc., April 1932, p. 182.

stomach,[48] and concentrated gastric juice administered intramuscularly.[49] The cases of patients who received liver therapy for nine and one-half, eight and seven years, respectively, have been described.[50] The potency of liver extract may be increased by incubation with gastric tissue[51] or gastric juice.[52] Some of the components of the vitamin B complex may play a part in the gastric formation of hematopoietically active substances.[53] Gastric juice from the fourth stomach of adult cattle is a source of the extrinsic factor.[54]

It has been suggested that intensive iron therapy in conjunction with the administration of liver substances may be of value in reducing the neurologic symptoms.[55]

Massive doses of liver extract may hasten the onset of the reticulocyte response within certain physiologic limits.[56] Among the types of

48. Wilkinson, J. F.: Antianaemic Principle in Stomach Tissue, Proc. Roy. Soc. Med. **26**:1341, 1933. Sturgis, C. C., and Isaacs, R.: Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract, Ann. Int. Med. **5**:131, 1931.

49. Morris, R. S.; Schiff, Leon; Burger, G., and Sherman, J. E.: A Specific Hematopoietic Hormone in Normal Gastric Juice; Preliminary Report, J. A. M. A. **98**:1080 (March 26) 1932.

50. Gibson, R. B., and Fowler, W. M.: Effects of Prolonged Liver Dietary in Pernicious Anemia: Case Reports of Three Patients Receiving Liver Therapy for Nine and a Half, Eight, and Seven Years, Respectively, Arch. Int. Med. **50**: 124, (July) 1932.

51. Walden, G. B., and Clowes, G. H. A.: Pernicious Anemia: Method Whereby Therapeutic Efficiency of Liver and Liver Fractions May Be Substantially Increased, Proc. Soc. Exper. Biol. & Med. **29**:873, 1932. Barnett, C. W., and Thebaut, W. M., Jr.: Treatment of Pernicious Anemia with Digested Liver, J. A. M. A. **99**:556 (Aug. 13) 1932. Conner, H. M.: Preparation of Liver and Stomach (Extralin) in the Treatment of Pernicious Anemia, M. Clin. North America **18**:385, 1934.

52. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Increased Potency of Liver Extract by Incubation with Human Gastric Juice, Proc. Soc. Exper. Biol. & Med. **30**:775, 1933.

53. (*a*) Conner, H. M.: Extract of Fish Liver in Treatment of Pernicious Anemia: Treatment of Pernicious Anemia with Diet Rich in Vitamines, M. Clin. North America **15**:463, 1932. (*b*) Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias; Activation of Yeast Derivatives with Normal Human Gastric Juice, New England J. Med. **207**:55, 1932. (*c*) Goodall, A.: Treatment of Pernicious Anaemia by Marmite, Lancet **2**:781, 1932.

54. Williams, H. A., and Vander Veer, J. B.: Demonstration of Anti-Anemic Factor in Bovine Gastric Juice, Proc. Soc. Exper. Biol. & Med. **29**:858, 1932.

55. Sargant, W.: Treatment of Subacute Combined Degeneration of Cord by Massive Iron Dosage, Lancet **1**:230, 1932.

56. Connery, J. E., and Goldwater, L. J.: Studies on Patients with Pernicious Anemia Treated with Massive Doses of Liver Extract: Effect on Reticulocytes, Red Cells, Hemoglobin and White Cells, J. Lab. & Clin. Med. **17**:1016, 1932.

liver found to be effective are preparations from cattle, horse,[57] fish,[58] pig and dog.[59]

Nuclear extractives from the red blood cells of fowl are active in inducing a remission when taken by mouth.[60] Autolyzed liver has been reported as being more active than fresh liver,[61] but recent work has not confirmed this.[62]

The intramuscular method of administration is preferred for those patients who are unable to retain food or who do not absorb material from the gastro-intestinal tract properly.[63]

Intra-ossal injection of liver has been suggested.[64]

Minot[65] emphasized the importance of giving medication on a quantitative basis, judging the requirements of each patient separately. Some patients require from two to three times the dosage of others.[66] Transfusion of blood is suggested when the blood count is very low and infection or other complication is present.[67] Dilute hydrochloric acid with meals is advocated only for those patients who have gastric distress after meals.[68] As a check for the efficiency of treatment of the

57. Meyer, A. E.; Richter, O., and Ivy, A. C.: Pernicious Anemia: Treatment with Equine Liver Extract Injectable Either Subcutaneously or Intravenously, Arch. Int. Med. **50**:538 (Oct.) 1932.

58. Davidson, L. S. P.: Treatment of Pernicious Anaemia with Fish-Liver Extract, Brit. M. J. **2**:347, 1932. Footnote 53*a*.

59. Strauss, M. B., and Castle, W. B.: Amount of Material Effective in Pernicious Anemia Present in Dog Liver, Proc. Soc. Exper. Biol. & Med. **31**:360, 1933.

60. Jones, N. W.; Phillips, B. I., and Larsell, O.: Hemopoietic Effect of Nuclear Extractives from Red Blood Cells of Fowl in Pernicious Anemia, Northwest Med. **31**:380, 1932.

61. Herron, W. F., and McEllroy, W. S.: The Use of Autolyzed Liver in the Treatment of Pernicious Anemia: A Preliminary Clinical Report, J. A. M. A. **100**:1084 (April 8) 1933.

62. Castle, W. B., and Strauss, M. B.: Effect of Autolysis on Potency of Liver in Treatment of Pernicious Anemia, J. A. M. A. **104**:798 (March 9) 1935.

63. Connery, J. E., and Goldwater, L. J.: Parenteral Use of Liver Extract in Treatment of Pernicious Anemia, J. A. M. A. **98**:1060 (March 26) 1932. Owen, A., and Anderson, D.: Pernicious Anemia Treated with Liver Extract Given Intramuscularly, M. J. Australia **2**:572, 1932. Alt, H. L.: Maintenance Dose of Parenteral Liver Extract in Treatment of Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **30**:565, 1933.

64. Josefson, Arnold: A New Method of Treatment—Intraossal Injections, Acta med. Scandinav. **81**:550, 1934.

65. Minot, G. R.: The Importance of the Treatment of Pernicious Anemia on a Quantitative Basis, J. A. M. A. **99**:1906 (Dec. 3) 1932.

66. Kloster, J.: Einige Erfahrungen über die Dosierung des Campolons bei der Biermerschen Anämie, Acta med. Scandinav. **79**:475, 1933.

67. Sturgis, C. C., and Isaacs, R.: Pernicious Anemia: Its Nature and a Consideration of Recent Advances in the Treatment of the Disease, California & West. Med. **39**:73, 1933.

68. Sturgis, C. C., and Isaacs, R.: Treatment of Pernicious Anemia, Northwest Med. **31**:1, 1932.

blood, Haden [69] recommended the determination of the size of the red blood cells. Treatment is inadequate as long as there is macrocytosis.

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

There appear to be five factors which may produce a macrocytic anemia. It is generally accepted that the substance necessary for the maturation of red blood cells is formed from the interaction of (1) an extrinsic factor (food) and (2) an intrinsic factor present in the stomach. The resulting product is (3) absorbed from the intestine, (4) stored in the liver and (5) released to the body tissues for utilization when needed. Any disturbance of this mechanism at the point indicated by the numbers will produce a macrocytic anemia.

Although vitamin B_2 has been proved not to be the extrinsic factor in pernicious anemia, a commercially prepared autolyzed yeast extract has been of value for treatment of macrocytic anemia of pregnancy, tropical anemia and experimental macrocytic anemia resulting from a deficient diet in vitamin B_2.[70] If for any reason, known or unknown, the intrinsic factor present in the stomach is diminished [71] or destroyed, a macrocytic anemia simulating pernicious anemia may develop. Cases of pernicious-like anemia have been reported following chronic alcoholism,[72] syphilis and cancer of the stomach,[73] gastrectomy [74] and

69. Haden, R. L.: Complete Treatment of Pernicious Anemia, Am. J. Digest. Dis. & Nutrition **1**: 628, 1934.

70. Wills, L.: Note on Use of Marmite (Yeast Extract) in Tropical Macrocytic Anemias, Including Pernicious Anemia of Pregnancy, Indian M. Gaz. **68**: 133, 1933; Treatment of Pernicious Anaemia of Pregnancy and "Tropical Anemia" with Special Reference to Yeast Extract (Marmite) as Curative Agent, Brit. M. J. **1**:1059, 1931. Witts, L. J.; Fairley, N. H., and Goodhar, G.: Discussion on Megalocytic Anemias of Tropical and Non-Tropical Countries, Proc. Roy. Soc. Med. **25**:1703, 1932. Wills, L., and Bilimoria, H. S.: Pernicious Anemia of Pregnancy: Production of Macrocytic Anemia in Monkeys by Deficient Feeding (Curative Effect of Marmite), Indian J. M. Research **20**:391, 1932. Rhoads, C. P., and Miller, D. K.: Production in Dogs of Chronic Black Tongue with Anemia, J. Exper. Med. **58**:585, 1933.

71. (*a*) Goldhamer, S. M., and Isaacs, R.: Rôle of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **31**:706, 1934. (*b*) Goldhamer, S. M.: Relationship Between Gastric Juice Volume and Erythropoiesis in Patients with Untreated Pernicious Anemia, ibid. **32**:376, 1934. (*c*) Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy: Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and Treatment of These Conditions, Am. J. M. Sc. **185**:539, 1933.

72. Torrey, R. G.: Anemia Due to Gastritis Occasioned by Alcoholism; Consideration of Cases of Purpura, Including Example of Purpura Apparently Secondary to Pernicious Anemia, M. Clin. North America **17**:603, 1933.

73. Conner, H. M., and Birkeland, I. W.: Coexistence of Pernicious Anemia and Lesions of Gastro-Intestinal Tract: Carcinoma of Stomach; Consideration of Twenty Cases: Eleven Reported, Ann. Int. Med. **7**:89, 1933.

(Footnotes continued on next page)

pregnancy.[71c] The occurrence of macrocytic anemia has also been reported in many instances in which there was a dysfunction of absorption from the intestinal tract. Obstruction of the small intestine, tapeworm, celiac disease, gastrocolic fistula and sprue have all been observed in association with macrocytic anemia.[75] Study of the bone marrow in some cases of sprue, during relapse and remission, revealed a striking similarity to the pathologic changes associated with pernicious anemia.[76]

Following the experimental work [77] which proved the liver to be the storehouse of the material necessary for the maturation of red blood cells there were several references to an anemia with a high color index occurring in association with disease of the liver.[78] There appears to

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74. Goldhamer, S. M.: The Pernicious Anaemia Syndrome in Gastrectomized Patients, Surg., Gynec. & Obst. **57**:257, 1933. Rowlands, R. A., and Simpson, S. Levy: Addisonian Anemia Following Gastrectomy and Gastro-Jejunostomy, Lancet **2**:1202, 1932. Ungley, C. C.: A Case of Complete Gastrectomy Followed by Pernicious Anaemia, Newcastle M. J. **12**:192 (Oct.) 1932.

75. Hurst, A. F.: Case of Addison's Anemia with Subacute Combined Degeneration of Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of Ileum, Guy's Hosp. Rep. **83**:47, 1933. Birkeland, I. W.: "Bothriocephalus Anemia"; Diphyllobothrium Latum and Pernicious Anemia, Medicine **11**:1, 1932. Mills, E. S.: Anaemia from Dibothriocephalus Latus, Canad. M. A. J. **25**:75, 1931. Magath, T. B.: Bothriocephalus Anemia (Anemia Caused by Diphyllobothrium Latum), Proc. Staff Meet., Mayo Clin. **5**:124, 1930. Vaughan, J. M., and Hunter, D.: Treatment by Marmite (Yeast Extract) of Megalocyte Hyperchromic Anemia Occurring in Idiopathic Steatorrhea (Celiac Disease), Lancet **1**:829, 1932. Fairley, N. H., and Kilner, T. P.: Gastro-Jejuno-Colic Fistula, with Megalocytic Anemia Simulating Sprue, ibid. **2**:1335, 1931. Barker, L. F.: A Few of the Cases Selected for Study on Ward Rounds Illustrating Method of Procedure, Internat. Clin. **3**:26, 1931. Rogers, L., and Cooke, W. E.: Resistant Sprue Anemia Yielding to Intravenous Liver Therapy, Brit. M. J. **1**:272, 1932. Vaidya, S. K.: Observations on Pernicious-Type Anemias in Tropics, and Disease Called Sprue, J. Trop. Med. **33**:265, 1930.

76. Rhoads, C. P., and Castle, W. B.: Pathology of Bone Marrow in Sprue Anemia, Am. J. Path. (supp.) **9**:813, 1933.

77. (*a*) Richter, O.; Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," Proc. Soc. Exper. Biol. & Med. **29**:1093, 1932. (*b*) Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Rôle of Liver in Hematopoiesis, Am. J. M. Sc. **188**:193, 1934.

78. Wintrobe, M. M., and Shumacher, H. S., Jr.: Occurrence of Macrocytic Anemia in Association with Disorder of Liver, Together with Consideration of Relation of This Anemia to Pernicious Anemia, Bull. Johns Hopkins Hosp. **52**: 387, 1933. Goldhamer, S. M.: Liver Extract Therapy in Cirrhosis of the Liver; Relation of Liver Dysfunction to Nonstorage of "Anti-Anemic" Substance in Producing a Blood Picture Resembling Pernicious Anemia in a Patient Secreting Free Hydrochloric Acid, Arch. Int. Med. **53**:54 (Jan.) 1934. Van Duyn, J.: Macrocytic Anemia in Disease of Liver, ibid. **52**:839 (Dec.) 1933. Wright, D. O.: Macrocytic Anemia and Hepatic Cirrhosis, Am. J. M. Sc. **189**:115, 1935. Wright, D. O.: Macrocytic Anemia in Banti's Disease, Ann. Int. Med. **8**:814, 1935. Footnote 77*b*.

be sufficient evidence that the intrinsic factor may be present in the stomach, but because of damage to the liver the hematopoietic substance cannot be stored and released to the body for utilization, and as a result macrocytic anemia develops.

The treatment of anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each given instance. If the intrinsic or extrinsic factor is absent, liver administered orally may be appropriate; however, if there is a disturbance of absorption or storage, parenteral therapy should be instituted.

ANEMIA OF PREGNANCY

Strauss [79] emphasized that the physiologic anemia of normal pregnant women consists of a steady decline in the red blood cell count and hemoglobin content from early in pregnancy until the end of the second trimester, after which no further change or a slight rise occurs. About ten days after parturition the blood returns to the level prior to pregnancy provided there is no defect in diet or gastric secretion. A study of the volume of the blood during pregnancy indicated that this condition is not anemia in the strict sense but merely hydremia.

Strauss stated further that a woman with one of any number of diseases which may cause anemia may become pregnant and the anemia associated with the pregnancy may be nothing more than a coincidence. This is true in cases of infection, leukemia and cancer. Moreover, pregnancy may be associated with toxemia, hemorrhage, nephritis and puerperal sepsis, any one of which may produce anemia.

When these known causes of anemia are disregarded, however, there still remain two types of anemia of pregnancy of unknown etiology. One is hypochromic (chlorotic or simple secondary anemia, idiopathic hypochromic anemia) and the other, macrocytic (pernicious).

Thirty patients with idiopathic hypochromic anemia of pregnancy, all of whom had a hemoglobin content of less than 45 per cent (Sahli), were studied from the standpoint of gastric secretory defects and the character of the diets of which they had partaken. It was found that all of these patients had anacidity or hypo-acidity or had been eating a diet which was inadequate in iron-containing foods. In some instances both the diet was poor and there was a deficiency of gastric acidity. Another factor in the production of anemia is the loss of hemoglobin-building material from the mother which must be used for synthesis of the fetal hemoglobin. When the patients were given 6 Gm. of iron and ammonium citrate daily there was a prompt return of the hemoglobin content and red blood cell count to normal.

79. Strauss, M. B.: Etiology and Treatment of Anemia in Pregnancy, J. A. M. A. **102**:281 (Jan. 27) 1934.

Ten patients with macrocytic anemia were studied by Strauss. These patients all had a red blood cell count under 2,500,000 per cubic millimeter, and, in addition to the usual symptoms of anemia, gastrointestinal complaints and fever were observed in a majority of them. Glossitis was present in 4 patients and splenomegaly in 2. One patient had mild combined degeneration of the spinal cord. The blood picture closely simulated that of true addisonian pernicious anemia. In 5 patients there was achlorhydria, in 4, hypochlorhydria, and in 1, normal acidity of the gastric juice, following the injection of histamine. All but 1 of these patients gave a history of a limited intake of food containing animal protein. The administration of 200 Gm. of beefsteak daily resulted in some improvement, but a greater effect was produced by giving 150 cc. of normal gastric juice incubated with the beefsteak. It was concluded that patients with this type of anemia have both defects in gastric secretion and diets which have a deficiency chiefly in animal protein. The former is an etiologic factor similar to that associated with true addisonian pernicious anemia. This type of anemia is relieved by the administration of liver extract, either orally or parenterally.

It has been determined [80] that pregnant women who have hypochromic anemia bear infants with a normal blood picture at birth. In the latter, however, there develops anemia of varying severity during the first year of life. The anemia of the mother may be corrected by iron therapy during pregnancy, in which case the infant will not have anemia after birth. It is believed that this form of anemia in the infant is due to the inability of the fetus to accumulate sufficient reserves of iron, owing to a deficiency of this element in the maternal organism.

The volume of the blood and plasma has been systematically studied in a number of women from early pregnancy throughout the puerperium.[81] The plasma volume was determined by means of the vital red technic. It was found that the volume of the blood and that of the plasma increase during the first trimester until by the thirteenth week the gain amounts to 16 and 18 per cent, respectively. There is an average increase of 23 per cent in the blood volume and of 25 per cent in the plasma volume at term. Partly on account of the increase in the blood volume, but especially on account of the tremendous amount of fluid in her tissues, the pregnant woman survives losses of blood which would be fatal to a nonpregnant person. There is a decrease of 16 per cent in both the blood and the plasma volume eight weeks post partum. Dieckmann and Wegner interpreted the increase in the volume of the

80. Strauss, M. B.: Anemia of Infancy from Maternal Iron Deficiency in Pregnancy, J. Clin. Investigation **12**:345, 1933.

81. Dieckmann, W. J., and Wegner, Carl R.: The Blood in Normal Pregnancy: I. Blood and Plasma Volumes, Arch. Int. Med. **53**:71 (Jan.) 1934.

blood and plasma as an attempt of the body to fill the vessels and as "probably a part of the mechanism required to permit proper fetal respiration."

ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

HEMOLYTIC JAUNDICE

Clinically, hemolytic jaundice of the congenital type is characterized by anemia, enlargement of the spleen, jaundice, a history of exacerbations and remissions, microcytosis, spherocytosis, increased fragility of the red blood cells and constant reticulocytosis.[82] The anemia, jaundice, splenomegaly and increase in the young red blood cells are probably secondary to the increased destruction of blood resulting from the abnormal fragility of the erythrocytes.[83] Often, hemolytic icterus is complicated with ulcers, osseous changes and gallstones.[84]

The etiology of the disease remains theoretical. The change in the size and shape of the red blood cells is thought by some to be a hereditary expression of the disease; others are of the opinion that the alteration in the red blood cells is due to lessened vitality of the cells; still others believe that there is a primary defect in the bone marrow, and, finally, some observers suggest that the small red blood cells and increased fragility are phenomena of regeneration secondary to the increased activity of the bone marrow.

Although microcytosis has been recognized in hemolytic jaundice for many years, it is only recently that spherocytosis has been emphasized in this condition, and it can best be shown by the increase in the volume-thickness index.[83] Normal erythrocytes, when placed in hypotonic salt solution, become progressively more spherical with practically no alteration in the diameter as the solution is made more hypotonic. Just preceding hemolysis the cells assume their most globular form. In congenital hemolytic jaundice many of the erythrocytes are already spherical and hence are nearer the point of hemolysis. It has been concluded from these experiments that there is a direct relation between the volume-thickness index and the fragility of the red blood cells.

Chronic cholecystitis and cholelithiasis have been reported in 68 per cent of the cases of hemolytic jaundice.[84b] The differential diagnosis is thus quite confusing. Congenital acholuric jaundice must also be

82. Barron, M.: Differential Diagnosis of Jaundice, with Special Reference to Congenital Hemolytic Jaundice, Minnesota Med. **15**:479, 1932.

83. Haden, R. L.: The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, Am. J. M. Sc. **188**:441, 1934.

84. (*a*) Cheney, W. F., and Cheney, G.: Chronic Hereditary Hemolytic Jaundice, with Report of Eight Cases and Notes on Measurement of Size of Erythrocytes, Am. J. M. Sc. **187**:191, 1934. (*b*) Custer, R. P.: Congenital (Familial) and Acquired Hemolytic Jaundice: Review of North American Literature for Late 1930 and 1931, Folia haemat. **48**:137, 1932.

differentiated from toxic hepatitis and hemolytic anemia due to various toxins and infections. There has been considerable controversy as to whether there is a syndrome of acquired hemolytic jaundice. It is felt that this disease is in reality an exacerbation of the congenital type.[85]

Treatment of this condition with preparations of iron and arsenic vitamins and irradiation of the spleen has proved to be of no value.[84a] The greatest success has been splenectomy.[86] Transfusions have been invaluable before and after surgical intervention, although occasionally transfusion may increase the hemolytic process.[87] The mortality rate reported by various investigators is less than 5 per cent.[86e] Within two weeks after the operation the blood count returns to normal limits[88] and the jaundice disappears.[86a] Examination of a stained blood film reveals persistent microcytosis.[86e] The abnormality of the fragility of the red blood cells also persists[89] with rare exceptions.[90] In the instances in which splenectomy fails, the diagnosis of familial hemolytic jaundice may be questioned.[91]

SICKLE CELL ANEMIA

In 1910 James B. Herrick[92] described a new entity characterized by certain clinical manifestations—sickle-shaped erythrocytes in the peripheral blood and severe anemia. Mason[93] in 1922 gave the condition the name sickle cell anemia, which is now generally accepted.

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85. Dawson, B. E.: Hume Lectures on Haemolytic Icterus, Brit. M. J. **1**: 921 and 963, 1931.

86. (*a*) Hargis, E. H., and Simon, H. E.: Splenectomy for Hemolytic Jaundice, South. Surgeon **1**:334, 1933. (*b*) Livingstone, J. L., and Edwards, H.: Acholuric Jaundice Treated by Splenectomy, Proc. Roy. Soc. Med. **26**:366, 1933. (*c*) Joyce, J. L., and Mills, J.: Three Cases of Familial Acholuric Jaundice, ibid. **26**:366, 1933. (*d*) East, T.: Acholuric Jaundice with Almost Normal Erythrocyte Fragility, ibid. **26**:365, 1933. (*e*) Pemberton, J. deJ.: Results of Splenectomy in Splenic Anaemia: Haemolytic Jaundice and Haemorrhagic Purpura, Tr. Am. S. A. **49**:346, 1931. (*f*) Thomson, A. P.: Acholuric Jaundice with Increased Fragility of Red Blood Corpuscles Appearing After Splenectomy, Lancet **2**:1139, 1933. (*g*) Harris, K. E.: Acholuric Jaundice Associated with Purpura, Proc. Roy. Soc. Med. **26**:369, 1933. (*h*) Else, J. E.: Familial Hemolytic Icterus, S. Clin. North America **13**:19, 1933. (*i*) Footnote 84.

87. Footnotes 84*a* and 85.

88. Footnote 86*f* and *g*.

89. Footnote 86*e* and *f*.

90. Joyce, T. M.: Hemolytic Jaundice, S. Clin. North America **13**:77, 1933.

91. Toland, C. G.: Fatal Hemolytic Crisis One Year Following Splenectomy for Splenic Anemia, West. J. Surg. **41**:91, 1933. Freund, M.: Hemolytic Jaundice Not Influenced by Splenectomy, Am. J. Dis. Child. **43**:645 (March) 1932.

92. Herrick J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517 (Nov. 15) 1910.

93. Mason, V. R.: Sickle Cell Anemia, J. A. M. A. **79**:1318 (Oct. 14) 1922.

A short time later Sydenstricker [94] and his associates demonstrated that this disease is not uncommon among members of the Negro race. A comprehensive review of the literature up to 1929 has been written by Steinberg.[95]

Corrigan and Schiller [96] reported 8 cases of sickle cell anemia and recorded the recognition of the disease in New England for the first time. They emphasized that the disease might masquerade under such diagnoses as rheumatic fever, tuberculosis, acute abdominal conditions, syphilis and obscure forms of anemia. As a relatively high percentage of Negroes have this type of anemia they urged the study of preparations of fresh blood when any of the aforementioned diagnoses are considered in patients of this race. In the case of 1 patient, aged 23, a necropsy was performed, and changes in the spleen and liver and marked hyperplasia of bone marrow were the prominent pathologic observations; the spleen, which weighed 0.87 Gm., is probably the smallest on record. As to treatment, Corrigan and Schuller concluded that a satisfactory form would probably not be developed until the mechanism causing the sickling was discovered. Transfusions of blood had only a temporary beneficial effect. Large doses of preparations of arsenic and iron and a high intake of vitamins are of no special value. One patient was given twenty-two consecutive daily injections of 5 cc. of liver extract without any appreciable effect being obtained on the reticulocyte count or the general blood picture. These authors reviewed the effect of splenectomy in patients with this disease who have splenic enlargement and stated that in more than half of them this operation was followed by freedom from symptoms and some improvement in the general blood picture, but the sickle cell trait remained unchanged. Lash [97] reported the case of a Negro primipara, aged 21, in whom death followed a long labor and cesarean section. Although the diagnosis was not made during life, the autopsy observations were characteristic of sickle cell anemia. The patient's spleen weighed 960 Gm., which is the largest reported in the literature. The baby survived, and moist preparations of fresh blood showed sickle cells after twenty-four hours.

Ching and Diggs [98] reported the case of a Negro girl, aged 18 years, with this condition in whom extensive clinical and hematologic studies

94. Sydenstricker, V. P.: Sickle Cell Anemia, South. M. J. **17**:177, 1924; Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12 (July 5) 1924.

95. Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876 (April) 1930.

96. Corrigan, J. C., and Shiller, I. W.: Sickle Cell Anemia: Report of Eight Cases, One with Necropsy, New England J. Med. **210**:410, 1934.

97. Lash, A. F.: Sickle Cell Anemia in Pregnancy, Am. J. Obst. & Gynec. **27**:79, 1934.

98. Ching, R. E., and Diggs, L. W.: Splenectomy in Sickle Cell Anemia: Report of a Case with Necropsy in an Adult on Whom Splenectomy Was Attempted, Arch. Int. Med. **51**:100 (Jan.) 1933.

were made over a period of two years and on whom a complete autopsy was performed. The patient received a transfusion of blood and was given a diet of liver. In addition, she was given sodium cacodylate, dilute hydrochloric acid and mercury and iodide tablets. This was followed by slow improvement. The authors expressed the belief, however, that no conclusions can be drawn as to the effect of liver or other therapy because too many antianemic measures were concurrently employed. A short time later the patient suffered a relapse, and an attempt was made to perform a splenectomy, but the spleen could not be found. This was readily explained at necropsy, for the fibrotic remnant of this organ was flattened out and was so firmly adherent to the diaphragm that it appeared to be a part of it. The authors concluded that the benefits of splenectomy have not yet been proved. If this procedure is to be given a further trial it should be attempted only in cases in which there is splenomegaly. This appears to be a logical statement because the removal of a small spleen may be of no value and in some instances, as in the authors' case, impossible.

Rosenfeld [99] reviewed the literature on sickle cell anemia in the white race. He regarded the report of Cooley and Lee [100] of a case of sickle cell anemia in a white child of Greek descent as the first case in which no reasonable suspicion can be raised of an admixture of Negro blood. The second case, in a white native-born American of Scotch-Irish parentage, reported by Sights and Simon,[101] Rosenfeld did not completely accept because the absence of data concerning the patient's family did not make it possible to exclude definitely the admixture of Negro blood. His own patient came from a family in which three generations had shown the sickling trait and five generations were known to be of the white race from a region where Negroes are practically unknown.

Lawrence,[102] Hunter [103] and others have reported a hereditary deformity of red blood cells occurring in both white persons and Negroes, characterized by elliptic and oval erythrocytes in the peripheral blood of otherwise normal persons. There is no evidence to indicate that this condition is related to sickle cell anemia, but the possibility should be considered.

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99. Rosenfeld, S., and Pincus, J. B.: The Occurrence of Sicklemia in the White Race, Am. J. M. Sc. **184**:674, 1932.

100. Cooley, T. B., and Lee, P.: Sickle Cell Anemia in a Greek Family, Am. J. Dis. Child. **38**:103 (July) 1929.

101. Sights, W. P., and Simon, S. D.: Marked Erythrocytic Sickling in a White Adult, Associated with Anemia, Syphilis and Malaria: Report of a Case, J. Med. **12**:177, 1931.

102. Lawrence, J. S.: Human Elliptical Erythrocytes, Am. J. M. Sc. **181**: 240, 1931.

103. Hunter, W. C.: Further Studies of White Family Showing Elliptical Erythrocytes, Ann. Int. Med. **6**:775, 1932.

APLASTIC ANEMIA

The literature, consisting mostly of reports of cases, is rather confused, as cases of true aplastic anemia, aleukemic leukemia, pernicious anemia and agranulocytosis are erroneously classified under this heading. Several reports deal with the diagnosis by means of biopsy of bone marrow. Among the etiologic agencies mentioned in the reports were arsphenamine, neoarsphenamine, arsenic, benzine, roentgen rays, sepsis lenta, intestinal stenosis, pregnancy and aleukemic leukemia as well as an idiopathic form.

Various forms have been described. Of the aplastic and hypoplastic myeloses, three groups can be distinguished: (1) partial—(*a*) erythropenic, (*b*) leukopenic and (*c*) thrombopenic; (2) mixed—(*a*) erythroleukopenic, (*b*) erythrothrombopenic and (*c*) leukothrombopenic and (3) total—erythroleukothrombopenic.[104]

In an analysis of 13 cases, Thompson, Richter and Edsall [105] found that 12 occurred in men. The age varied from 25 to 70 years (average, 46). The first symptoms were weakness and pallor coming on insidiously and rarely purpuric manifestations. The average red blood cell count remained about 1,500,000 per cubic millimeter, with a hemoglobin content of 20 per cent (Sahli). Severe leukopenia was the rule, and platelets numbered less than 50,000 per cubic millimeter. The reticulocytes varied from 0.1 to 18 per cent. The bone marrow was not always aplastic, however, and hypoplasia or even hyperplasia of the elements was noted.

ACUTE HEMORRHAGE

Acute massive hemorrhage is primarily a vascular problem.[106] The arterial, venous and capillary blood pressure decreases. The flow of blood decreases, the heart rate increases, an increased amount of epinephrine is discharged into the circulation, the spleen contracts, pouring its stored blood into the general circulation, and local areas of vasoconstriction occur. The respiratory rate increases owing to local asphyxia in the respiratory center and to the lactic acid coming into the circulation from the tissues as tissue fluid enters the capillaries as a result of the fall in capillary blood pressure. Urinary secretion decreases. Adolphe, Gerbasi and Lepore [106a] studied the rate of dilution

104. Baserga, A.: Le mielosi aplastiche: contributo sperimentale ed anatomopatologico, Haematologica, I. Arch. **13**:481, 1932.

105. Thompson, W. P.; Richter, M. N., and Edsall, K. S.: An Analysis of So-Called Aplastic Anemia, Am. J. M. Sc. **187**:77, 1934.

106. (*a*) Adolph, E. F.; Gerbasi, M. J., and Lepore, M. J.: Rate of Entrance of Fluid into the Blood in Hemorrhage, Am. J. Physiol. **104**:502, 1933. (*b*) Neumann, B.: Experimentelle Beiträge zum Studium des Blutverlustes: II. Die Veränderungen der Eiweisswerte und des osmotischen Druckes im Serum und das Auftreten junger Erythrocyten, Arch. f. klin. Chir. **172**:529, 1932.

of the blood in dogs after a hemorrhage of one third of the blood volume. Dilution was completed in about twenty-two minutes, or at a rate of 0.25 cc. per kilogram per minute. Analytic methods for the study of changes in tissue fluids were unsatisfactory. Neumann [106b] stressed the importance of circulatory adjustments and called attention to the character of the fluid which diluted the blood, namely, a fluid low in protein and relatively high in salt.

Studies of changes in the size of the red blood cells following acute hemorrhage have yielded contradictions. Camero and Krumbhaar [107] bled dogs of 60 per cent of the blood volume, and the following day bled them of 30 per cent of the original volume. A definite increase of the mean diameter of the red cells (from 7.6 to 8.3 microns) and of the mean corpuscular volume (from 52 to 87 cubic microns) was observed. Leichsenring and Honig [108] bled dogs of only 25 per cent of the blood volume on two successive days, then of 50 cc. weekly, and observed a progressive decrease in both the diameter of the red cells and the mean corpuscular volume during the following six months. Murphy and Fitzhugh [109] reported an increase in the mean corpuscular volume after acute hemorrhage and a decrease after chronic hemorrhage in human beings.

Lindenbaum [110] studied the bone marrow at frequent intervals after a single hemorrhage of two fifths of the blood volume in rabbits. Within the first hour after the hemorrhage there was an increase in the number of mitotic figures in the hemocytoblasts, myelocytes and erythroblasts, which, along with the markedly increased cellularity of the bone marrow, reached a peak on the fourth day after the hemorrhage. The number of megakaryocytes increased in a similar manner. Lindenbaum expressed the belief that posthemorrhagic leukocytosis is due to displacement of these cells by the hyperplasia occurring in the bone marrow. The bone marrow remained hyperplastic after twenty-two days. Lewin [111] confirmed Lindenbaum's observations on the bone

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107. Camero, A. R., and Krumbhaar, E. B.: The Effect of Experimental Massive Hemorrhages on the Size of the Red Blood Cell in Dogs, Am. J. Physiol. **103**:407, 1933.

108. Leichsenring, J. M., and Honig, H. H.: Blood Regeneration Studies: I. Changes in the Volume, Number and Size of the Erythrocytes in Hemorrhagic Anemia, Am. J. Physiol. **98**:636, 1931.

109. Murphy, W. P., and Fitzhugh, G.: Red Cell Size in Anemia: Its Value in Differential Diagnosis, Arch. Int. Med. **46**:440 (Sept.) 1930.

110. Lindenbaum, J. S.: Das Knochenmark in den ersten Stunden und Tagen nach dem Aderlass, Folia haemat. **39**:501, 1930.

111. Lewin, O.: Die morphologischen Veränderungen in den blutbildenden Organen nach akuten Blutverlusten. Experimentelle Untersuchungen, Beitr. z. path. Anat. u. z. allg. Path. **88**:394, 1932.

marrow and studied the changes in the liver, spleen and lymph nodes. Associated with hyperplasia of the marrow, Lewin observed proliferation of the reticulo-endothelial system and, contrary to previous studies, myeloid metaplasia of the spleen. In both of these studies fixed tissue sections of the marrow were employed. Using films made of suspensions of bone marrow stained with Wright's stain, Steele [112] studied the ratio of megaloblasts, normoblasts, reticulocytes and mature red cells in the bone marrow of rabbits after acute and chronic hemorrhage and poisoning with phenylhydrazine. On the fifth day following a single hemorrhage of one third of the blood volume the number of normoblasts increased to twice the normal proportion while the percentage of mature red cells decreased a corresponding amount, the number of the other two types of cells remaining unchanged.

Gordon [113] studied litter mate rabbits subjected to the same hemorrhage (one sixty-fourth of the body weight). The red cell count fell to the same minimum level on the day following the bleeding in all the rabbits and returned to the normal level in the same time. The number of reticulocytes reached the peak on the fifth day in all the rabbits and varied individually only between 6.6 per cent and 7.2 per cent.

Eaton and Damren [114] estimated the duration of the existence of the red cell in the circulation at about eight days on the basis of the interval of time between recurring peaks in the reticulocyte count following a hemorrhage and on the basis of a mathematical relationship between two types of reticulocytes.

Miller and Rhoads [115] made an interesting morphologic observation in chronic hemorrhagic anemia. Rabbits were bled continually in sufficient amounts to maintain a 50 per cent hemoglobin level, and the hemoglobin thus removed was reinjected into the same animal subcutaneously. The blood of such rabbits showed a high color index and a mean corpuscular volume above the normal level compared with that of animals which were bled but which did not receive the hemoglobin by injection and in which the color index and mean corpuscular volume were low. At autopsy a megaloblastic marrow was found in the first animals compared with the normoblastic marrow present in

112. Steele, B. F.: The Effects of Blood Loss and Blood Destruction upon Erythroid Cells in the Bone Marrow of Rabbits, J. Exper. Med. **57**:881, 1933.

113. Gordon, A. S.: The Quantitative Nature of the Red Cell Response to Single Bleeding, Proc. Soc. Exper. Biol. & Med. **31**:563, 1934.

114. Eaton, P., and Damren, F. L.: A Method for Determining the Life Duration of the Erythrocyte: II. The Rate of Red Cell Production After Hemorrhage, South. M. J. **23**:395, 1930.

115. Miller, D. K., and Rhoads, C. P.: The Effect of Hemoglobin Injections on Erythropoiesis and Erythrocyte Size in Rabbits Rendered Anemic by Bleeding, J. Exper. Med. **59**:333, 1934.

animals subjected to hemorrhage only. A similar predominance of megaloblasts was reported by Steele [112] in rabbits after poisoning with phenylhydrazine.

From the hematologic point of view treatment is seldom necessary after even a moderately acute hemorrhage in an otherwise normal person. Pepper and Farley [116] stated that after the removal of 500 cc. of blood from a normal donor of blood all signs of increased regeneration of red cells disappear in one week's time. The reserve stores of the body are adequate to care rapidly for a single moderate loss of blood.

Additional information concerning anemia associated with chronic hemorrhage will be found under the heading "iron deficiency anemia."

CANCER

Although anemia [117] is common in association with cancer, it is by no means always present, nor does it necessarily localize the lesion. If the material necessary for the maturation of red blood cells cannot reach the bone marrow macrocytic anemia develops; [118] if there is a disturbance of iron metabolism (failure of absorption or chronic hemorrhage) microcytic anemia appears. Thus, the color index may be high or low. In the majority of instances mild leukocytosis is present. The platelets may be increased, decreased or normal. The treatment of anemia associated with cancer depends on the etiology. The anemia may be aided by antianemic therapy,[119] but it cannot be eliminated without removal of the primary causal factor.

INFECTION

The normal blood picture is a reflection of the balance between the production and the destruction of cells. As a result of infection there may be an increased destruction of red blood cells or a decreased production, and hence anemia.[120] As a compensatory measure for the increased demand of red blood cells by the reaction of the body immature

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116. Pepper, O. H. P., and Farley, D. L.: Practical Hematological Diagnosis, Philadelphia, W. B. Saunders Company, 1933.

117. Morrison, M.: Analysis of Blood Picture in One Hundred Cases of Malignancy, J. Lab. & Clin. Med. **17**:1071, 1932.

118. Conner, H. M., and Birkeland, I. W.: Coexistence of Pernicious Anemia and Lesions of Gastro-Intestinal Tract: Carcinoma of Stomach; Consideration of Twenty Cases; Eleven Reported, Ann. Int. Med. **7**:89, 1933. Musser, J. H.: Anemias Simulating Pernicious Anemia, Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America **6**:409, 1931.

119. Goldhamer, S. M., and Bethell, F. H.: The Value of Iron Therapy in Secondary Anemia, to be published.

120. Markowitz, B.: The Hematopoietic System and Infection, Am. J. Clin. Path. **2**:449, 1932.

red blood cells are released into the peripheral circulation. Many of the young cells are hypochromic, as they have had insufficient time to take up iron.[121] Secondary anemia is thus produced.

In addition to microcytic anemia most infections are characterized by leukocytosis. However, the total number of white blood cells is not as important as the type of leukocyte. The more severe the infection, the more immature are the myeloid cells.[122] As the infection subsides older cells reappear.[123] A useful interpretation of the severity and progress of infection can thus be ascertained. The reappearance of eosinophils is likewise to be interpreted as a favorable sign in a subsiding infection. The secondary anemia and hemogram are of clinical value in determining the presence and course of infection, but they do not aid in localizing the site.

ENDOCRINE DISTURBANCES

The coexistence of anemia and myxedema has been observed by a number of investigators. It may be of the primary [124] or of the secondary [125] type and may be related directly to the thyroid dysfunction or may exist as an independent condition. To be on the safe side it is best to treat the two conditions separately.

A specific blood picture related to hyperthyroidism has been reported; however, there appears to be a wide divergence of opinion concerning this. A relative and absolute increase in lymphocytes [126] has been observed in some instances, and in others, a relative and absolute monocytosis,[127]

121. Kugelmass, I. N., and Lampe, M.: Mechanism of Anemia Associated with Infection in Infancy and in Childhood, Am. J. Dis. Child. **43**:291 (Feb.) 1932.

122. Weiss, A.: Blood Picture in Infectious Disease, J. Lab. & Clin. Med. **16**:655, 1931.

123. Eisenberg, A. A., and Nemans, H. S.: Value of Schilling Hemogram in Infections: Preliminary Report Based on Three Thousand Five Hundred Cases, Am. J. Surg. **21**:56, 1933.

124. Lisser, H., and Anderson, E. M.: Three Cases of Adult Myxedema in Women, Reported for Purpose of Calling Attention to Their Widely Different Symptomatology and Clinical Findings, Endocrinology **15**:365, 1931. Davis, C. L.: Myxedema with Associated Primary Type of Anemia, Pennsylvania M. J. **34**: 873, 1931. Means, J. H.; Lerman, J., and Castle, W. B.: Coexistence of Myxedema and Pernicious Anemia, New England J. Med. **204**:243, 1931. Kunde, M. M.; Green, M. F., and Burns, G.: Blood Changes in Experimental Hypo- and Hyperthyroidism (Rabbit), Am. J. Physiol. **99**:469, 1932.

125. (*a*) Lerman, J., and Means, J. H.: The Treatment of Anemia of Myxoedema, Endocrinology **16**:535, 1932. (*b*) McCullagh, E. P., and Dunlap, J. H.: Blood picture in Hyperthyroidism and in Hypothroidism, J. Lab. & Clin. Med. **17**: 1060, 1932.

126. Gottlieb, R.: Blood Studies in Hyperthyroidism, J. Lab. & Clin. Med. **19**: 371, 1934. Footnote 125*b*.

127. Hertz, S., and Lerman, J.: Blood Picture in Exophthalmic Goitre: Changes Resulting from Iodine and Operation; Study by Means of Supravital Technic, J. Clin. Investigation **11**:1179, 1932.

while a third investigator [128] stated that the differential blood picture in hyperthyroidism is normal and hence of no clinical importance from a diagnostic standpoint.

DISEASES OF THE KIDNEYS

In cases of chronic nephritis 56 per cent of the patients may have anemia (hemoglobin content less than 70 per cent, red blood cells less than 4,000,000 per cubic millimeter). In about 90 per cent of the cases there is a close correlation between the degree of retention of nitrogen and anemia.[129] For prognosis, a 40 per cent concentration of hemoglobin has about the same prognostic significance as a blood creatinine value of 5 mg. per hundred cubic centimeters or of advanced neuroretinitis.[130] Three cases of nephritis have been noted in which anemia was the predominant symptom, without edema or hypertension.[131] In cases of acute and chronic glomerular nephritis, essential hypertension (nephrosclerosis), and polycystic kidney and after unilateral nephrectomy the condition of the blood is closely correlated with the degree of impairment of renal function, as measured by Mosenthal's criteria of the volume and specific gravity of the urine during twenty-four hours.[132] The anemia may be masked by associated congestive heart failure.[131] The degree of anemia is also correlated with the degree of impairment of renal function as measured by the test of urea clearance.[133] Retention of nitrogen may occur, however, without anemia.[134] The bone marrow may be fatty and relatively aplastic. The red blood cells tend to be small, and the color index is about 0.9.[135]

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128. Jackson, A. S.: Blood Picture in Six Hundred Cases of Goitre; Especial Reference to Effect of Iodine and Thyroidectomy, J. A. M. A. **97**:1954 (Dec. 26) 1931.

129. Brown, G. E.,, and Roth, G. M.: Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

130. (*a*) Berg, B. N.: Blood in Chronic Nephritis Associated with Nitrogen Retention, Am. J. M. Sc. **164**:88, 1922. (*b*) Parsons, L., and Ekola-Strolberg, M.: Anemia in Azotemia, ibid. **185**:181, 1933. (*c*) Scarlett, E. P.: Significance of High-Grade Anemia in Chronic Nephritis, with Report of Four Cases, ibid. **178**:215, 1929.

131. Ashe, B.: Hemoglobin Percentage and Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension, Arch. Int. Med. **44**:506 (Oct.) 1929.

132. Mosenthal, H. O., and Lewis, D. S.: A Comparative Study of Tests for Renal Function, J. A. M. A. **67**:933 (Sept. 23) 1916.

133. Van Slyke, D. D., et al: Observations on Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy, Medicine **9**:257, 1930.

134. Aubertin, C., and Yacoel, J.: L'anémie dans le néphrite azotemigue, Presse méd. **28**:461, 1920.

135. Klemperer, P., and Otani, S.: "Malignant Nephrosclerosis" (Fahr), Arch. Path. **11**:60 (Jan.) 1931. Footnotes 130*b* and *c* and 131.

The anemia is more common in the nephrotic stage of glomerular nephritis than in lipoid nephrosis.[136] The associated infection in children may be a factor in producing the anemia.[137] The associated conditions, such as epistaxis and gross hematuria, may be contributing factors.[138] During the terminal stage there may be mild neutrophilic leukocytosis, occasionally with an increase in the number of eosinophils. According to some workers, leukocytosis is present in uremia only if there is associated infection.[139] There appears to be no direct correlation between the hemorrhagic diathesis and the number of blood platelets.[136]

EFFECT OF METALS, DRUGS AND RADIATION

LEAD

The hematologic changes associated with lead poisoning continue to receive considerable attention. Punctate basophilia (stippling) of the red blood cells in the peripheral blood stream is, in the absence of marked anemia, good evidence of exposure to lead.[140] Badham [141] reported that stippling is usually correlated with excretion of lead. Stippling occurs in other disorders of the blood, such as pernicious anemia.[140a] It has also been noted as an early sign of benzene poisoning by McCord,[142] and Litzner [143] reported its presence in 8 cases of anemia associated with contracted kidney in the primary or secondary stage with retention of nitrogen in which no exposure to lead had occurred.

Several papers have been devoted to the nature of polychromatophilia of the red blood cells and the relationship of diffuse basophilia, punctate basophilia and the reticulum as revealed by supravital staining. According to Cooke and Hill,[144] polychromatophilia is due to the presence of the remains of the cytoplasm of the erythroblast, which in the immature red blood cell has not completely disappeared. Supravital

136. Wilbur, D. L., and Brown, G. E.: Blood in Lipoid Nephrosis, with Special Reference to Absence of Anemia, Arch. Int. Med. **45**:611 (April) 1930.

137. Clausen, S. W.: Parenchymatous Nephritis as a General Systemic Disorder, Am. J. Dis. Child. **29**:581 (May) 1925.

138. Pákozdy, K.: Ueber den Zusammenhang zwischen den Nierenkrankheiten und den hämorrhagischen Diathesen, Ztschr. f. klin. Med. **112**:124, 1929.

139. Footnotes 130*b*, 134, 136 and 137.

140. (*a*) Nelson, W. T.; Lockwood, L., and Mackay, K.: The Incidence of Punctate Basophilia, M. J. Australia **2**:317, 1932. (*b*) Lane, R. E.: Rôle of Punctate Basophilia in the Control of Industrial Plumbism, J. Indust. Hyg. **13**:276, 1931.

141. Badham, C.: Basophilia and Lead Excretion in Lead Poisoning, M. J. Australia **2**:816, 1933.

142. McCord, C. P.: Industrial (Benzol) Benzene Poisoning: Presence of Immature Red Cells in the Blood Stream, Warthin Anniv. Vol. 1927, p. 39.

143. Litzner, S.: Ueber das Vorkommen basophil getüpfelter roter Blutkörperchen bei Schrumpfnieren, Med. Klin. **29**:81, 1933.

144. Cooke, W. E., and Hill, C. F.: II. Microscopical Studies in Pernicious Anemia, J. Roy. Micr. Soc. **51**:14, 1931.

stains, such as brilliant cresyl blue, act on the surface of the red blood cell in such a way that the stain enters the cell, precipitating this diffuse cytoplasmic material into clumps. Whether the basophilia appears diffuse or punctate depends on the condition of the surface of the red blood cell and on the staining methods[145] During reticulocytosis following hemorrhage in rabbits Key [146] long ago demonstrated that the stippled cell was a reticulocyte with abnormal staining properties due to the effect of lead. Whitby and Britton [145a] confirmed these observations in a study of the influence of lead during anemia caused by phenylhydrazine. These last two observers, as well as others, have pointed out that the sum of the stippled cells and the diffusely basophilic cells is approximately equal to the reticulocyte count. Accordingly, stippled cells appear to be immature red blood cells the basophilic staining properties of which have been altered by the effect of lead or other agents. Since lead acting in vitro on red blood cells does not cause stippling,[145a] the alteration must occur in the bone marrow. Stippling, however, is not seen in fixed sections of bone marrow.[147] Several observers [148] have reported that the degree of stippling in relation to diffuse basophilia in a blood film depends on the rate of drying of the film and on the stain employed.

The mechanism of the action of lead on the red blood cell was carefully studied by Aub and his associates.[149] They concluded that lead combined in the circulation with the phosphates of the red cell, thus damaging the lipoidal cell membrane and producing a shrunken, brittle and more fragile red blood cell. Maxwell and Bischoff [145b] made a further study of this chemical phenomenon.

Brookfield [145c] in an investigation of the treatment of cancer in human beings and McLean [150] of its value in animals with cancer studied the

145. (*a*) Whitby, L. E. H., and Britton, C. J. C.: The Relation of Stippled Cell and Polychromatic Cell to Reticulocyte, Lancet **1**:1173, 1933. (*b*) Maxwell, L. C., and Bischoff, F.: The Reaction of Lead with Constituents of Erythrocyte, J. Pharmacol. & Exper. Therap. **37**:413, 1929. (*c*) Brookfield, R. W.: Blood Changes Occurring During Course of Treatment of Malignant Disease by Lead with Special Reference to Punctate Basophilia and the Platelets, J. Path. & Bact. **31**:277, 1928.

146. Key, J. A.: Lead Studies: III. Blood Changes in Lead Poisoning in Rabbits with Especial Reference to Stippled Cells, Am. J. Physiol. **70**:86, 1924.

147. Seifert, G., and Arnold, A.: Zell Veränderungen in Knochenmark, Blut und Milz bei experimenteller Bleivergiftung, Arch. f. Hyg. **99**:272, 1928.

148. Brückner, H.: Arbeiten über die basophile Substanz in den jugendlichen roten Blutkörperchen; über die Wirkung der Fixierung und über den Einfluss der Wasserstoffionenkonzentration der Farblösungen auf die Darstellbarkeit der basophilen Substanz, Arch. f. Hyg. **99**:236, 1928. Footnote 145*a*.

149. Aub, J. C., and Reznikoff, P.: Lead Studies: III. The Effect of Lead on Red Blood Cells; Chemical Explanation of Reaction of Lead with Red Blood Cells, J. Exper. Med. **40**:189, 1924.

150. McLean, J. A.: Changes in the Blood and Hematopoietic Tissue in Experimental Lead Poisoning, M. J. Australia **2**:1, 1930.

effects of Blair Bell's colloidal lead preparations administered parenterally. Brookfield observed an anemia, occasionally severe, in most of his patients. The red blood cell count fell as much as 1,000,000 per cubic millimeter during the first hour after an injection, and at this time a high degree of poikilocytosis was observed both in fixed films and in the wet preparations. A reticulocyte response followed, associated with the presence of a large number of stippled red cells. The white blood cells and blood platelets showed no constant change. In rabbits McLean found a parallel decrease in red blood cells and hemoglobin and a moderate number of reticulocytes and stippled red cells. The cell volume and the blood volume showed a marked decrease. Leukocytosis was present during the first few days. The neutrophils reached a peak on the first day, and the lymphocytes and monocytes on the second day. Myelocytes were numerous during the first two days, while the eosinophils increased on the third day. There was a sharp transient increase in blood platelets on the first day after the injection of a colloidal lead preparation. The bone marrow at first showed granulocytic hyperplasia. Many of the cells contained pyknotic nuclei and other signs of degeneration. Later these cells were replaced by an erythroblastic hyperplasia. Deposits of hemosiderin were prominent. The spleen and lymph nodes in surviving animals were hyperplastic, and in those which died, aplastic. Seifert and Arnold [147] reported similar findings.

The increase in the excretion of hematoporphyrin reported in cases of plumbism in human beings was observed experimentally by Liebig.[151]

Kasahara and his associates [152] have made interesting studies of lead poisoning arising in infants caused by lead contained in Japanese toilet powders and cosmetics. A large amount of lead was found in the milk of the infants' mothers. Anemia with stippled cells was present in these children, and toxic granules were observed in the neutrophils.[153] Davidson [154] reported cases of lead anemia caused by an excessive amount of lead in the drinking water.

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151. Liebig, H.: Ueber die experimentelle Bleihämatoporphyrie, Arch. f. exper. Path. u. Pharmakol. **125**:16, 1927.

152. Kasahara, M., and Nosu, S.: Studien über die Bleivergiftung im Säuglings- und Kleinkindesalter: I. Klinische und experimentelle Untersuchungen über den Uebergang von Blei in die Milch, Ztschr. f. Kinderh. **55**:577, 1933. Kasahara, M., and Nagahama, M.: II. Die Bleianämie im Säuglings- und frühen Kindesalter, ibid. **55**:583, 1933.

153. Kasahara, M., and Nagahama, M.: Das Auftreten der pathologisch granulierten Leukocyten bei infantiler Bleivergiftung, Folia haemat. **53**:37, 1934.

154. Davidson, L. S. P.; Fullerton, H. W.; Rae, H. J., and Henderson, A.: Lead Poisoning in the North-East of Scotland, Lancet **2**:374, 1933. Davidson, L. S. P.: Macrocytic Hemolytic Anemia, Quart. J. Med. **1**:543, 1932.

The presence of stippled red blood cells associated with mild anemia is presumptive evidence of lead poisoning. Removal from exposure and symptomatic treatment are indicated.

Aluminum exerts an effect similar to that of lead on the red blood cells and organs.[155]

ARSENIC

Severe blood dyscrasias are among the rare complications of the arsphenamine therapy of syphilis. McCarthy and Wilson[156] reviewed the literature thoroughly in 1932, collecting 79 cases which fall into three groups: (1) those of thrombocytopenia, with or without neutropenia, in which the prognosis is uniformly good; (2) those of granulocytopenia, with four fatalities among 12 cases, and (3) those of aplastic anemia with a mortality of 80 per cent. Concerning the first group, Mu[157] reported a study of the blood platelet count following injections of neoarsphenamine. In 10 patients in whom there was no reaction the blood platelet count decreased to less than one half of the normal number during the first few hours after the injection and returned to a higher than normal level on the following day. The simple purpuric reactions occur typically within a few hours of a treatment, and recovery is rapid. Peripheral destruction of the blood platelets without damage to the hematopoietic organs seems to be the most likely explanation. Since McCarthy and Wilson's article appeared, other cases have been reported.[158] Blood dyscrasia has been noted after all types of arsphen-

155. Seibert, F. B., and Wells, H. G.: The Effect of Aluminum on Mammalian Blood and Tissues, Arch. Path. **8**:230 (Aug.) 1929.

156. McCarthy, F. P., and Wilson, R., Jr.: The Blood Dyscrasias Following the Arsphenamines, J. A. M. A. **99**:1557 (Nov. 5) 1932.

157. Mu, J. W.: The Effect of Neoarsphenamine on Number of Blood Platelets, Proc. Soc. Exper. Biol. & Med. **26**:407, 1929.

158. (*a*) Loveman, A. B.: Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines, Ann. Int. Med. **5**:1238, 1932. (*b*) Rich, M. L.: An Unusual Hematologic Reaction to Neoarsphenamine, J. A. M. A. **101**:1223 (Oct. 14) 1933. (*c*) Stephens, D. J.: Aplastic Anemia Following Sulpharsphenamine with Recovery, Am. J. Syph. & Neurol. **18**:24, 1934. (*d*) Knott, F. A.: A Case of Toxic (N. A. B.) Aplastic Anemia: Death from Pneumonia When Recovering After Fifty-Two Blood Transfusions, Guy's Hosp. Rep. **84**:32, 1934. (*e*) Kostoulas, A.: Hémorragies des muqueuses post- "neo-606" et sulfarsénobenzoliques, Bull. Soc. franç. de dermat. et syph. **40**:771, 1933. (*f*) Chevallier, P.; Colin, M.; Bernard, J., and Ely, Z.: Sur les formules sanguines des syndromes hémorragiques toxiques. A propos de six cas d'hémorragies post-arsénobenzoliques recueillis en un an, Sang **6**:917, 1932. (*g*) Preti, L.: Anémie aplastiche semplici: eritro- e plastrinopeniche, Riforma med. **49**:199, 1933. (*h*) Bennett, J. B., and Prichard, J. F.: Stomatitis with Aplastic Anemia Occurring During the Treatment of Syphilis with Neoarsphenamine, Case Report, Texas State J. Med. **29**:40, 1933. (*i*) Hawkins, H. F.: Acute Aplastic Anemia

(Footnote continued on next page)

amine therapy with or without coincident bismuth or mercury therapy and in all stages of syphilitic infection.

Moore and Keidel [159] reported a study of exfoliative dermatitis following the injection of arsphenamine. Among 11 cases leukopenia was noted in 6, neutropenia in 10 and eosinophilia in 9. These changes in the leukocytes were present at the time of the first mild untoward reactions, before the severe disturbances following subsequent injections occurred. These authors advocated an examination of the blood in the presence of the mildest symptoms following injection before continuing arsenical treatment. In nearly all of the cases of blood dyscrasia associated with the injection of arsphenamine reported in the literature adequate premonitory symptoms have been present. If the symptoms had been heeded it might have been possible to avoid subsequent serious results. In some cases reported another type of arsenical preparation has subsequently been well tolerated, but in Grund's case [158j] there developed the same hemorrhagic reaction to bismarsen as had previously been given to neoarsphenamine.

At autopsy aplastic bone marrow is usually found, but, as in the case of poisoning created by benzene, regenerating marrow has been observed in a patient dying of some intercurrent toxic infectious process as a result of the poor resistance associated with the neutropenic state.[160]

To the presence of the benzene ring in the arsphenamine molecule has been attributed the cause [161] of blood dyscrasias. The rarity of such reactions detracts from such a theory, and from what is known of the transformation and fate of arsphenamine in the body Voegtlin [162] expressed a doubt that the arsphenamine molecule is broken down to a benzene ring in the body. Because of the tendency of these severe reactions to occur after many injections have been given and often following one of the first few treatments immediately after a rest period in the course of treatment, Moore and Keidel [159] suggested that the bone marrow somehow becomes sensitized to the particular arsenical preparation in use. This remains a speculation. Only 1 case of severe depression of the bone marrow associated with inorganic arsenic poisoning

with Recovery, ibid. **28**:822, 1933. (*j*) Grund, J. L.: Purpura Hemorrhagica with Profuse Bleeding from the Mucous Membranes Following the Treatment of Syphilis with Bismarsen, New England J. Med. **211**:443, 1934.

159. Moore, J. E., and Keidel, A.: Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis, Arch. Int. Med. **27**:716 (June) 1921.

160. Stephens, D. J.: Aplastic Anemia Occurring During Treatment of Syphilis with Arsphenamines, Am. J. Syph. **15**:333, 1931.

161. Farley, D. L.: Depressed Bone Marrow Function from Arsphenamines, Including Type of So-Called Agranulocytosis, Am. J. M. Sc. **179**:214, 1930.

162. Voegtlin, C.: Personal communication quoted by Hamilton.[165]

has been reported,[163] although in 28 cases of inorganic arsenic poisoning caused by arsenic orchard spray left in a cider barrel reported by Lawson, Jackson and Cattanach [164] leukopenia, neutropenia and eosinophilia were noted in the survivors between the fifth and twelfth day following the poisoning.

The best treatment is prevention, which is usually possible. Infections must be carefully avoided and combated, and transfusions of blood are recommended to tide the patient over until the function of the bone marrow returns to normal.

Arsine, an occasional cause of industrial poisoning, produces rapid and severe anemia as a result of a combination of this substance with the hemoglobin in the red blood cells, leading to rapid hemolysis. Hemolysis is a prominent feature of this condition. Leukocytosis and the presence of immature cells of both the red and the white blood cell series are usually found.[165]

BENZENE

In acute benzene poisoning no morphologic changes occur in the blood, although a patient surviving an acute massive exposure may subsequently show the hematologic changes found in chronic poisoning. Hamilton [166] has reviewed the extensive literature concerning the action of benzene on animals and on human beings as a result of occupational exposure and in the treatment of leukemic states. Individual idiosyncrasy plays a large rôle in the response to benzene poisoning, and variations in the size of the dose, the route of absorption and the duration of its action in industrial exposure introduce limitless variables. The extensive experience reported shows that no limited hematologic alteration in man or in animals can be ascribed to the effects of benzene. As with all toxic agents, stimulation and depression are observed depending on the size of the dose and the rate of absorption. This is manifested in the various elements of the blood and of the hematopoietic organs. In the blood an increase in the number of one or more of its elements (red blood cells, white blood cells, platelets) or depression of one or

163. Wheelihan, R. Y.: Granulocytic Aplasia of Bone Marrow Following Use of Arsenic, Am. J. Dis. Child. **35**:1032 (June) 1928.

164. Lawson, G. B.; Jackson, W. P., and Cattanach, G. S.: Arsenic Poisoning, J. A. M. A. **85**:24 (July 4) 1925.

165. Hamilton, A.: Industrial Poisoning in the United States, New York, The Macmillan Company, 1929, (*a*) p. 220; (*b*) p. 243 and 272; (*c*) p. 307; (*d*) p. 280; (*e*) p. 420; (*f*) p. 431; (*g*) p. 332; (*h*) p. 357; (*i*) p. 405; (*j*) p. 493. (*k*) Fretwurst, F.; Hurwitz, S., and Rosenbaum, R.: Zur Frage der Arsenwasserstoffvergiftung mit besonderer Berücksichtigung der Blutveränderungen (nach Tierexperimenten), Ztschr. f. klin. Med. **123**:703, 1933.

166. Hamilton, A.: Benzene (Benzol) Poisoning, Arch. Path. **11**:434 (March) and 601 (April) 1931.

more of these elements is observed. In the early or mild stage a marked increase in the immaturity of the circulating cells often occurs, followed, after continued influence of the poison, by a marked decrease in the number of these blood cells and by the absence of signs of rapid regeneration. The same situation exists in the hematopoietic organs, varying from hyperplasia to aplasia of one or more of the bone marrow elements as well as of the lymphatic and reticulo-endothelial apparatus. The classic picture of aplastic anemia in chronic industrial benzene poisoning is, perhaps, most common: severe anemia with a normal color index, without an increase in the number of immature red blood cells and, usually, with complete absence of such cells. Leukopenia, neutropenia and thrombocytopenia are usually present. Variation in the severity of these abnormalities is associated with great variation in the clinical picture of aplastic anemia, agranulocytic angina or thrombocytopenia purpura haemorrhagica alone or progressing from simple mild purpura to severe aplastic anemia. The occasional observation of hyperplastic bone marrow at autopsy associated with a premortem aplastic blood picture [167] is not disconcerting in the light of a variety of studies on animals and human beings reported for a variety of aplastic conditions of the blood [168] in which the organism has not survived long enough to benefit by the regeneration occurring in the bone marrow.

Two cases of leukemia have been reported following long mild exposure to benzene,[169] and Lignac [170] observed aleukemic and leukemic lymphoblastomas in mice after benzene poisoning.

Since Hamilton's review in 1930 there have appeared only confirmation and further elucidation of the knowledge of the effect of benzene on the hematopoietic system.[171]

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167. Andersen, D. H.: Benzol Poisoning with Hyperplasia of Bone Marrow, Am. J. Path. **10**:101, 1934.

168. Footnotes 158*c* and 167.

169. Delore, P., and Borgomano: Leucémie aiguë au cours de l'intoxication benzénique: Sur l'origine toxique de certaines leucémies aiguës et leurs relations avec les anémies graves, J. de méd. de Lyon **9**:227, 1928. Weil, P.: La leucémie post-benzolique, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:193, 1932.

170. Lignac, G. O. E.: Die Benzolleukämie bei Menschen und weissen Mäusen, Klin. Wchnschr. **12**:109, 1933.

171. (*a*) Osgood, E. E.: Action of Benzol, Roentgen-Rays and Radium on Blood and Blood Forming Organs, Ann. Int. Med. **6**:711, 1932. (*b*) Merklen, P., and Israel, L.: Intoxication par le benzol: aleucie hémorragique, autrement dit "hypoleucie hémorragiques avec anémie," Sang **8**:700, 1934. Harkins, H.: Granulopenia and Agranulocytic Angina, J. A. M. A. **99**:1132 (Oct. 1) 1932. Weiskotten, H. G.: The Normal Life Span of the Neutrophil (Amphophil) Leukocyte (Rabbit): Action of Benzol, Am. J. Path. **6**:183, 1930. Lemétayer, E.: Action du benzène sur les leucocytes; Recherches expérimentales chez de cheval, Compt. rend. Soc. de biol. **114**:1284, 1933. Reich, C., and Reich, C.: Hematopoietic Response of

(Footnote continued on next page)

In the prevention of severe poisoning in industry neutrophilic leukocytosis [166] and an abnormal number of polychromatophilic red blood cells [142] in the circulation are the signs of the early stimulant phase of benzene poisoning which demand removal from exposure to benzene and correction of the working conditions. Benzene notably requires a long time to develop its full toxic effect; symptoms of severe poisoning often occur several months after exposure has ceased. The treatment is that for all aplastic conditions: symptomatic care and repeated transfusions.

GOLD

It is interesting that severe reactions of the types (thrombopenic purpura, granulocytopenia and aplastic anemia) occurring after arsphenamine therapy have also been observed following the injection of gold salts intravenously. Gold salts are little used in this country, but Dameshek [172] reported a case and reviewed the literature, collecting 8 cases, 1 of thrombopenia, 1 of granulocytopenia and 6 of aplastic anemia. Reports of 2 other cases [173] have appeared. Dyscrasia following treatment with gold compounds probably exonerates benzene from any etiologic rôle in the similar reactions to arsphenamine. General care and repeated transfusions are the only treatment available. The prognosis, of course, depends on the severity of the depression of bone marrow.

OTHER METALS AND POISONS

Bismuth is in common use in the therapy of syphilis. It is not ordinarily given intravenously and no cases of blood dyscrasia following

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the Rat to Injections of Pentnucleotide, and Its Relation to the Treatment of Agranulocytosis, Am. J. M. Sc. **187**:71, 1934. Beyer, G.: Chronische Benzolvergiftung bei Kaninchen (Beobachtungen am Blutbild), Ztschr. f. d. ges. exper. Med. **91**:410, 1933. Schillowa, A.: Veränderungen bei chronischer Benzolvergiftung (Experimentelle Untersuchung an Kaninchen), Folia haemat. **49**:447, 1933. Müller, E.: Durch Benzol erzeugte Thrombopenie: Ein Beitrag zur Frage der Benzolschädigungen beim Kaninchen, Beitr. z. path. Anat. u. z. allg. Path. **86**:273, 1931. Thompson, W. P.; Richter, M. M., and Edsall, K. S.: An Analysis of So-Called Aplastic Anemia, Am. J. M. Sc. **187**:77, 1934. Dassen, R.: Intoxicación benzólica crónica? Sindrome hemorrágico de la mucosa respiratoria (nariz y bronquios): Anemia aguda post-hemorrágica en un anémico crónico. Aleucia hemorrágica final. Curación, Semana méd. **2**:230, 1933.

172. Dameshek, W.: Aplastic Anemia Following the Treatment of Lupus Erythematosus with Gold Sodium Thiosulphate, With a Review of the Literature of the Hematological Reactions Following Gold Therapy, New England J. Med. **210**:687, 1934.

173. Jullien, W.: Aleucie hémorragique observée au cours d' un traitement par la crisalbine: Evolution favorable, Bull. et. mém. Soc. méd. d. hôp. de Paris **50**:174, 1934. Ameuille, P.; Kudelski, C., and Joseph, R.: Aleucie hémorragique d'apparition retardée observée au cours d'un traitement par la crisalbine, ibid. **49**:1428, 1933.

its use have been reported in the literature. The internal use of bismuth subnitrate may lead to methemoglobinemia through reduction of the nitrate to nitrite in the intestine.[174]

Mercury is likewise in common use, but no clear cases of hematopoietic reaction to its use have been reported.[175] Dalla Torre[176] reported a case of severe anemia with signs of regeneration in the peripheral blood which followed intensive treatment with inunctions of mercury in a syphilitic patient in whom two years previously there had developed a pallor during arsphenamine therapy. This patient also had acute mercurial poisoning with stomatitis and nephritis. In industrial exposure to mercury vapor neurologic and renal manifestations predominate, but mild anemia with a low color index and evidences of regeneration may appear.[165b]

Polycythemia has been produced in rats with cobalt.[177] In rabbits germanium dioxide leads to dehydration which is manifested by loss of weight and an increase in the concentration of the blood.[178] Hamilton reported polycythemia followed by anemia in industrial vanadium poisoning[165c] and leukocytosis during an attack of brass-founder's ague (zinc poisoning).[165d]

No deleterious influence of di-nitrophenol, recently incriminated in agranulocytic angina, was observed in the blood or hematopoietic organs of dogs by Tainter and his associates.[179]

Among reactions to volatile industrial poisons Hamilton reported: for methyl alcohol, polycythemia, leukocytosis and lymphopenia;[165e] for ethyl ether in young women, polycythemia and leukocytosis,[165f] for phosgene, an increase in both red and white blood cells followed by anemia,[165g] and for hydrogen sulphide, neutrophilic leukocytosis.[165h] Asphyxia without formation of sulphemoglobin occurs in acute hydrogen sulphide poisoning.[180]

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174. Roe, H. E.: Methemoglobinemia Following the Administration of Bismuth Subnitrate: Report of Fatal Case, J. A. M. A. **101**:352 (July 29) 1933.

175. Herzog, F., and Roscher, A.: Zur Klinik und Pathogenesis der Kollargolintoxikation beim menschen, Virchows Arch. f. path. Anat. **236**:361, 1922.

176. dalla Torre, G.: Anemia grave da intossicazione mercuriale, Riforma med. **48**:1926, 1932.

177. Orten, J. M.; Underhill, F. A.; Mugrage, E. R., and Lewis, R. C.: Blood Volume Studies in Cobalt Polycythemia, J. Biol. Chem. **99**:457, 1933.

178. Hueper, W. C.: The Effect of Overdoses of Germanium Dioxide upon the Blood and Tissues of Rabbits, Am. J. M. Sc. **181**:820, 1931.

179. Tainter, M. L.; Cutting, W. C.; Wood, D. A., and Proescher, F.: Di-nitrophenol: Studies of Blood, Urine and Tissues of Dogs on Continued Medication and After Acute Fatal Poisoning, Arch. Path. **18**:881 (Dec.) 1934.

180. Harrop, G. A., Jr., and Waterfield, R. L.: Sulphemoglobinemia, J. A. M. A. **95**:647 (Aug. 30) 1930.

Anemia and relative lymphocytosis supposedly due to exposure to gasoline fumes were reported in chauffeurs by Espeut and Salinger.[181] Hemolytic hyperchromic anemia with leukopenia involving both the granular and the lymphatic elements with rapid regeneration was produced in rabbits on inhalation of petroleum benzene by Schustrow and Salistowskaja.[182] Hamilton [165] reported a similar condition in industrial gasoline poisoning.

A group of substances act on the blood by converting hemoglobin into methemoglobin. The nitroderivatives and aminoderivatives of benzene are prominent members of this group.[163] In the presence of industrial exposure the methemoglobin-containing red cells are destroyed in sufficient numbers to produce hemolytic anemia with marked signs of regeneration. In such chronic conditions neutropenia is common. Voegtlin and his associates [183] made a careful study of tri-nitrotoluene poisoning in dogs and exposed employees. Fragmentation and phagocytosis of the red cells containing modified hemoglobin seemed to be the mechanism of this anemia. A majority of the exposed workers were anemic and their blood showed signs of rapid regeneration. Nitrites in general [174] and potassium chlorate lead to the formation of methemoglobin. Acetanilid, acetphenitidin and similar compounds in the excessive doses taken by addicts cause methemoglobinemia. If excessive doses are taken over a long period of time severe anemia with signs of regeneration may develop. Large doses, however, do not cause the formation of methemoglobin;[184] excessive continuous use seems necessary,[185] and even then severe anemia is rare. The relationship to sulphemoglobinemia remains obscure, for excessive use of acetanilid as often leads to sulphemoglobinemia as to methemoglobinemia.[180] The intestinal tract, liver [186] and spleen seem to play an important rôle in this condition. It is obvious that the usual acid hematin method of estimation of the hemoglobin content gives no idea of the oxygen-carrying power of the blood in these cases.[187] Reduction in the red blood cells or alteration in the leukocytes is rarely observed.

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181. Espeut, G., and Salinger, J.: Veränderungen des Blutbildes bei Kraftfahrern (Benzolschädigung?), Deutsche med. Wchnschr. **56**:360, 1930.

182. Schustrow, N., and Salistowskaja, E.: Das Blut bei der Benzinintoxikation, Deutsches Arch. f. klin. Med. **150**:271, 1926.

183. Voegtlin, C.; Hooper, C. W., and Johnson, J. M.: Tri-Nitro-Toluene Poisoning: Its Nature, Diagnosis and Prevention, J. Indust. Hyg. **3**:239, 1921.

184. Helms, S. T.: Some Facts Concerning the Pharmacological and Physiological Action of Acetanilide, J. Am. Pharm. A. **22**:1093, 1933.

185. Fischer, L. C.: Chronic Acetanilide Poisoning, J. A. M. A. **100**:736 (March 11) 1933.

186. Todd, A. T.: The Relationship of Sulphemoglobinemia to Hepatic Deficiency with Report of a Case, Am. J. M. Sc. **171**:635, 1926.

187. Dieckmann, W. J.: Methemoglobinemia, Arch. Int. Med. **50**:574 (Oct.) 1932.

In connection with the excessive use of acetanilid Schilling [188] observed "inner bodies" in the red cells which were thought to be areas of methemoglobin in the cell. These bodies were more numerous following splenectomy. In dogs fed acetanilid these bodies were not demonstrable in the blood unless the spleen was removed. Harrop and Waterfield [189] were likewise unable to produce sulphemoglobin in dogs without splenectomy. Zadek and Burg [189] reported a case similar to Schilling's and also found these bodies in the blood of two persons with ill-defined hematopoietic diseases after splenectomy without addiction to drugs. Pyrodine produced the same appearance [190] in the red cells of rabbits and dogs in vivo associated with hemolytic anemia with hyperplastic bone marrow and in the red cells of dogs and human beings in vitro. Phenylhydrazine depends on this hemolytic action for its therapeutic value in polycythemia.[191]

Normal propyldi-sulphide and related compounds contained in onions [192] are among the most recently studied hemolytic agents.

RADIATION

Martland [193] has summarized his experience with internal radiation by alpha particles. His description of osteitis caused by radiation is of importance hematologically. In the first stage the bone marrow is closely packed with promyelocytes, erythroblasts and hemocytoblasts. Eosinophilic myelocytes are prominent, whereas the neutrophils are scarce. Since the granulocytic cells are formed extravascularly, leukopenia without immature forms develops. In the red cells megaloblasts predominate, and macrocytes enter the general circulation. At this stage the peripheral blood shows hyperchromic anemia, with many immature red cells, leukopenia and neutropenia. There is no icterus, and the number of platelets is normal. In the second stage a patchy inflammatory replacement

188. Schilling, V.: Ueber einen als Herzfehler erscheinenden Fall von "Innenkörperanämie" aufgedeckt als chronische Antifebrinvergiftung und Coffeinsucht, Ztschr. f. klin. Med. **108**:709, 1928.

189. Zadek, I., and Burg, K.: Innenkörperanämien, Folia haemat. **41**:333, 1930.

190: Bratley, F. G.; Burroughs, H. H.; Hamilton, D. M., and Kern, C.: The Effect of Pyrodin Poisoning on Blood and Hemolytopoietic System, with Especial Reference to Formation of Heinz-Ehrlich Bodies in Vivo and Vitro, Am. J. M. Sc. **182**:597, 1931.

191. Hurwitz, S. H., and Levitin, J.: The Value of Phenylhydrazine in the Treatment of Polycythemia Vera, Am. J. M. Sc. **177**:309, 1929.

192. Gruhzit, O. M.: Anemia of Dogs Produced by Feeding of Whole Onions and of Onion Fractions, Am. J. M. Sc. **181**:812, 1931; Anemia in Dogs Produced by Feeding Disulphide Compounds, ibid. **181**:815, 1931.

193. Martland, H. S.: The Occurrence of Malignancy in Radioactive Persons; General Review of Data Gathered in Study of Radium Dial Pointers, with Special Reference to Occurrence of Osteogenic Sarcoma and Interrelationship of Certain Blood Diseases, Am. J. Cancer **15**:2435, 1931.

fibrosis of the bone marrow occurs which is difficult to distinguish from sarcoma. In these areas eosinophilic myelocytes, lymphocytes and plasma cells predominate. In the third stage the marrow is replaced by a fibrous acellular tissue. Microcytic anemia, without signs of regeneration, and leukopenia probably appear. Leukemia as well as osteogenic sarcoma has several times been observed. This type of industrial poisoning has been eliminated by prohibiting the use of the lips in pointing the brush in the painting of luminous dials. Barker,[194] from measurements of the amount of emanation present in rooms in which dials are painted, calculated that there is no danger of pathologic effects. Other workers have demonstrated the adequacy of present protective measures in handling radioactive materials,[195] in which the penetrating gamma rays are the usual source of danger. Dangerous exposure to radioactive materials was formerly common.[196] Hematologic alterations in miners of radioactive ores have been reported by Woldrich.[197] Fatal absorption of alpha rays from drinking radioactive water has occurred.[198]

The penetrating gamma rays from roentgen rays seldom give rise to occupational disease with the precautions prevalent at present.[199] However, the toxic granules in the leukocytes which appear during the roentgen treatment of leukemia [200] have been reported in the neutrophils of the blood of radiologists.[201] Very small doses of roentgen rays in man or animals lead to transient leukocytosis due to lymphocytosis. Therapeutic doses of roentgen rays may cause a transient increase in the number of neutrophils, but in this case lymphopenia is usually present and neutropenia appears later. During the phase of recovery eosinophilia is common. Often the platelets decrease in number. With large

194. Barker, H. H.: Radon Ingestion and Its Possible Health Dangers, Am. J. Roentgenol. **31**:673, 1934.

195. Schlundt, H.; McGavock, W., Jr., and Brown, M.: The Dangers of Refining Radioactive Substances, J. Indust. Hyg. **13**:117, 1931. Kaye, G. W. C.; Gell, G. E., and Binks, W.: Protection of Radium Workers from Gamma Radiation, Brit. J. Radiol. **8**:6, 1935.

196. Mottram, J. C.: Red Cell Blood Content of Those Handling Radium for Therapeutic Purposes, Arch. Radiol. & Electroth. **25**:194, 1920. de Laet, M.: La pathologie professionelle due aux corps radioactifs., Ann. de méd. lég. **8**:443, 1928.

197. Woldrich, A.: Die Blutveränderungen der Radiumarbeiter Joachims-Thals, Med. Klin. **27**:17, 1931.

198. Loeb, L. B.: The Nature, Effects and Menace of Radium Poisoning in Water, Water Works Eng. **87**:217, 1934; Chem. Abstr. **28**:2611, 1934.

199. Mottram, J. C.: Some Blood Examinations of X-Ray Workers, Brit. J. Radiol. **5**:156, 1932.

200. Bethell, F. H.: The Effect of Irradiation on the White Blood Cells in Chronic Myelogenous Leukemia, J. A. M. A. **104**:147 (Jan. 12) 1935.

201. Hirschfeld, H., and Moldawsky, J.: Ueber das Vorkommen der sogenannten toxischen (pathologischen) Leukocytengranulation bei Radiologen und radiologischen Hilfskräften, Klin. Wchnschr. **11**:1919, 1932.

doses of roentgen rays many degenerated white blood cells are seen in the circulation. No constant effect on the red cells has been observed. In chronic mild exposure to roentgen ray neutropenia, lymphocytosis and eosinophilia are the usual changes.[116] Massive irradiation in animals produces an aplastic bone marrow and aplastic anemia,[202] although Martland expressed the opinion that radiation osteitis in human beings caused by roentgen rays is a different reaction from that produced by the internal action of alpha particles.

The recent use of a thorium dioxide solution intravenously to obtain roentgen visualization of the liver, spleen and other viscera led to a study of the latent effects of this procedure on these organs. Tripoli [203] did not find pathologic changes in any organ with the minimal dose required for visualization in a wide variety of animals. No permanent damage occurred after much larger doses. Lambin,[204] however, using in rabbits about twice the smallest doses employed by Tripoli, after many months observed atrophy of the spleen, periportal fibrosis of the liver and aplasia of the bone marrow with an aplastic blood picture. Pohle and Ritchie [205] have confirmed Lambin's observations, using a smaller dose of thorium dioxide solution.

INFLUENCE OF IRON

RÔLE OF IRON IN THERAPY

Iron today occupies a place among that select group of preparations which have stood the test of worth. The modern view of iron in therapy may be said to have had its origin in the attempt to reconcile the experience of countless clinicians in the successful treatment of chlorosis with inorganic iron and the doctrine of Bunge [206] that the metal in such a state could not be absorbed and could not contribute to the manufacture of hemoglobin. Yet Bunge may be considered the father of the present conception of deficiency of iron as a primary cause of anemia. He and Abderhalden [207] were able to show that lactating animals store relatively large quantities of iron during the latter period of gestation and that

202. Footnotes 171*a* and 193.

203. Tripoli, C. J., and von Haam, E.: The Effects of Toxic and Non-Toxic Doses of Thorium Dioxide in Various Animals, Proc. Soc. Exper. Biol. & Med. **29**:1053, 1932.

204. Lambin, P.: Aspects histologiques de la fixation du dioxyde de thorium dans les organes, Compt. rend. Soc. de biol. **109**:66, 1932.

205. Pohle, E. A., and Ritchie, G.: Histological Studies of Liver, Spleen and Bone Marrow in Rabbits Following the Intravenous Injection of Thorium Dioxide, Am. J. Roentgenol. **31**:512, 1934.

206. Bunge, G.: Lehrbuch der physiologischen und pathologischen Chemie, ed. 4, Leipzig, F. C. W. Vogel, 1898.

207. Abderhalden, E.: Ztschr. f. phys. Chem. **26**:498, 1899.

this reserve supply is gradually depleted during lactation, which, if unduly prolonged, results in anemia. Whereas men came readily to disbelieve Bunge's view that inorganic iron was unabsorbable, on the other hand, his contention that such iron could take no part in the building of hemoglobin left its mark for many years, both on clinical teaching and on scientific investigation. Thus, in 1920 Nägeli [208] wrote that in his opinion chlorosis was due to a sluggishness of the hematopoietic process rather than to a lack of iron and that the benefits of the metal in medicinal form were due to its irritant and stimulative effect either directly on the bone marrow or through an indirect action. This conception of the stimulative effect of iron in medicinal form in the absence of its actual requirement for the formation of blood has by no means disappeared from present-day medical thought, and, as we shall point out later, has been utilized recently by Josephs in his explanation of the effect of iron on a certain type of anemia of infants. Among those who disagreed with the views of Nägeli was the French clinician Richaud,[209] who believed that inorganic iron was actually used for the synthesis of hemoglobin when administered in the treatment of chlorosis. He recognized two types of iron deficiency anemia: the first, the result of a dietary lack of the element, and the second, the result of impairment of absorption and utilization of the iron in food. In the latter group he placed chlorosis.

The skepticism toward the efficacy of iron in medicinal form which developed during the first and second decades of the present century and continued until a comparatively recent date was no doubt due to three contributing factors: The first was the gradual disappearance of chlorosis, the disease par excellence which yielded to iron therapy. The second was the use of iron in the treatment of a great variety of conditions, such as pernicious anemia and leukemia, in which it was of no possible benefit. The third, and of great importance, was the practice of administering iron in comparatively minute doses. It was felt, following the teaching of Bunge and Abderhalden, that since inorganic iron could take no part in the formation of blood the metal should be given either in complex organic form or in very small doses for its indirect or stimulating effect. In the past century iron was given in much larger amounts, and no doubt there were some clinicians who never adopted the fashion of minute dosage. To whom to give credit for priority in the restoration of iron to its proper place in therapeutics is impossible to determine. Arneth [210] in 1925 recalled that he had advocated large doses of reduced iron (from 0.75 to 0.9 Gm. daily)

208. Nägeli, O.: Zur Frage der Eisenwirkung bei Anämien, speziell bei Chlorose, Schweiz. med. Wchnschr. **50**:661, 1920.

209. Richaud, A.: La question du fer médicamenteux, Paris méd. **10**: 268, 1920.

210. Arneth: Zur Eisentherapie, Deutsche med. Wchnschr. **51**:1115, 1925.

twenty years before and that his views are contained in his textbook published in 1907. Alder [211] reported the treatment of a number of patients with chlorosis with reduced iron in pills containing 0.1 Gm., of which he gave from three to ten daily, depending on the severity of the anemia. He believed that the iron acted as an irritant on the blood-forming organs. Lindberg [212] was apparently the first to use reduced iron in really large doses. He administered 1 Gm. three times a day with excellent results, to four groups: (1) patients with anemia following influenza (epidemic of 1917-1918); (2) patients with anemias of the puerperium; (3) patients with "benign anemia of unknown origin," and (4) patients with chlorosis. He found no instances of gastrointestinal intolerance to this dosage.

Probably of greatest influence on present practice were the contributions of Meulengracht [213] and Barkan.[214] The former used, among other preparations, reduced iron (from 0.5 to 1 Gm. three times a day) in the successful treatment of anemia of chronic hemorrhage, simple anemia associated with achylia gastrica and chlorosis. He found large doses especially beneficial in diseases of the two latter groups. He noted that iron was ineffective in the treatment of anemia associated with infection, nephritis and malignant processes and was useless after acute hemorrhage because of the tendency toward spontaneous regeneration of the blood. Barkan treated patients with typical chlorosis with reduced iron (from 1 to 3 Gm. daily). He believed that the iron was converted to ferric chloride by the gastric hydrochloric acid and that the astringent action of the salt irritated the intestinal mucosa and so led to absorption. With the cure of anemia, according to him, the intestine became less susceptible to irritation, and consequently no cumulative absorption of iron with possible toxic effects occurred.

Recognition of the probable influence of the gastric acidity on the absorption of reduced iron led to investigations of the relative availability of bivalent and trivalent iron compounds. Heubner [215] reported that he detected no evidence of absorption of ferric iron from the gastrointestinal tract of dogs, the ferrous form alone being absorbed. Later [216]

211. Alder, A.: Zur Dosierung des Eisens, die Vorzüge hoher Dosen, Schweiz. med. Wchnschr. **50**:663, 1920.

212. Lindberg, G.: Ueber Anämie nach Influenza, nebst einigen Bemerkungen zur Eisentherapie der Anämien, Acta med. Scandinav. **56**:162, 1922.

213. Meulengracht, E.: Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, Acta med. Scandinav. **58**:594, 1923.

214. Barkan, G.: Therapie der Anämien mit grossen Eisengaben, Klin. Wchnschr. **2**:1748, 1923.

215. Heubner, W.: Bemerkung zur Eisentherapie, Ztschr. f. klin. Med. **100**: 675, 1924.

216. Heubner, W.: Ueber "organische" Eisenpräparate, Klin. Wchnschr. **5**: 588, 1926.

he investigated various preparations of organic iron. The nature of the organic radicle he found to be of little importance, protein derivatives being unnecessary. Of much greater significance was the valence of the iron, since only ferrous compounds were absorbed. Wiechowski [217] also concluded on the basis of experimental work that ferrous compounds alone were efficacious. Medicinal preparations, he warned, should be scrutinized carefully for possible oxidation to the trivalent form. He found little justification for parenteral administration of iron, as the ferrous preparations for use by mouth are so readily available. He advocated the use of reduced iron since the excess of the metal prevented oxidation by the gastric hydrochloric acid beyond the bivalent stage. Posener,[218] similarly influenced by the work of Heubner, concluded that reduced iron was of no benefit in the treatment of anemia associated with gastric anacidity. He believed that all organic preparations before absorption must be converted to ferrous chloride, and he stated that of available commercial preparations at least 90 per cent were either useless or superfluous. Deserving of special attention at this point are the work and views of Starkenstein. He grouped preparations of iron into four classes:[219] (1) true organic and inorganic acid iron salts (ferrous), which alone of the iron cations exhibits a pharmacodynamic effect; (2) complex compounds of the type of citric, malic and acetic acid combined with iron, which likewise have a strong pharmacodynamic effect, due, however, not to the action of iron cations but to the iron acting as an anion; (3) ferric salts, including ferric hydroxide, which, so far as their action depends on absorption from the gastro-intestinal tract, are entirely ineffective and (4) organic iron-containing compounds of the type of hemoglobin and the ferrocyanides, which also possess no pharmacodynamic effect. For therapeutic purposes, according to Starkenstein, only those preparations of iron should be employed which either are ferrous compounds or become so in the stomach. Compounds of which the iron tends spontaneously to assume the ferric form should be avoided. The medicinal form of choice, he said,[220] is ferrous chloride (free from trivalent iron). He recommended its use in place of reduced iron because its absorption is not dependent on the gastric acidity, because the digestive process in the stomach is not deprived of hydrochloric acid, which is the case when acid is required for chemical inter-

217. Wiechowski, W.: Die Eisentherapie im Lichte der neueren Forschung, Med. Klin. **23**:1765, 1927.

218. Posener, K.: Ueber die theoretischen Grundlagen der Eisentherapie, Therap. d. Gegenw. **68**:541, 1927.

219. Starkenstein, E.: Die derzeitigen pharmakologischen Grundlagen einer rationellen Eisentherapie, Klin. Wchnschr. **7**:217 and 267, 1928.

220. Starkenstein, E.: Therapeutischer Wert und chemische Wertigkeit der Eisenpräparate, Therap. d. Gegenw. **69**:394 and 451, 1928.

action with reduced iron and, finally, because small doses of ferrous chloride are always as effective as the largest doses of reduced iron, even when the latter is given to persons secreting an abundance of hydrochloric acid. To iron as a medicine Starkenstein [221] attributed three functions: (1) a catalyst for respiration of tissue through its presence in cytochrome; (2) a building stone for hemoglobin, and (3) a stimulant to the blood-forming organs. He pointed out that in many cases of apparent deficiency of iron the administration of a preparation of the metal is without effect since the real fault may be either an endocrine disorder or avitaminosis.

To Starkenstein and Heubner is due credit for a great forward step in the still meager knowledge of the processes involved in the assimilation and utilization of iron. Moreover, by their emphasis on the value of ferrous compounds they have made an important contribution to the rational therapy of anemia. It is now agreed by most observers, including Reimann in Germany, Davidson and Witts in Great Britain and Minot in the United States, that in terms of quantity administered simple ferrous compounds, such as the chloride, carbonate and sulphate, are the most effective forms of medicinal iron. However, to regard trivalent iron as totally inactive would require denial of the testimony of clinicians and investigators too numerous to mention. We shall refer only to the observations of Meulengracht,[213] who obtained equally good results with either colloidal ferric hydroxide or reduced iron, and to those of Mitchell and Vaughn,[222] who in treating the milk anemia of the albino rat found that ferric compounds were more efficacious than the bivalent form of iron. The poor showing of the ferrous salts in the latter authors' experiments was probably due to their comparative freedom from copper contamination.

THE IRON DEFICIENCY ANEMIAS

From the primary consideration of iron as a therapeutic agent we transfer attention to those conditions in which its use may be attended with benefit. It is customary to group such conditions under the general classification of iron deficiency, although so far as anemia in human beings is concerned such a designation is no more than an assumption, albeit a logical one. Aside from that due to chronic or recurrent bleeding, the iron deficiency anemias are linked definitely to age and sex. They tend to occur in infancy, in the female sex at puberty, in connection with pregnancy and throughout middle life in association with secretory dysfunction of the stomach.

221. Starkenstein, E.: Neue pharmakologische Richtlinien für die Eisentherapie, Med. Klin. **23**:111, 1927.

222. Mitchell, H. S., and Vaughn, M.: Relation of Inorganic Iron to Nutritional Anemia, J. Biol. Chem. **75**:123, 1927.

ANEMIA DUE TO CHRONIC HEMORRHAGE

In temperate climates the most common of all cases of anemia of adults are those due wholly or in part to an abnormal loss of blood, and the majority of these are caused by uterine hemorrhage, bleeding hemorrhoids and bleeding peptic ulcer. Such conditions should offer no great difficulty in diagnosis. During recent years attention has been given to another source of bleeding which may easily be overlooked. We refer to diaphragmatic hernia of the stomach. Möller [223] pointed out the common occurrence of anemia in this condition, and Segal [224] reported 5 cases of diaphragmatic hernia in which no symptoms were present except those attributable to anemia. He suggested as causes of bleeding passive congestion of the herniated portion of the stomach as the result of angulation of veins or pressure on them, ulcer due to varicosities from congestion or disturbed arterial supply. Bock, Dulin and Brooke [225] reported 10 cases of the same condition with surgical notes on 2 and an autopsy diagnosis on 3 others. In their cases the cause of bleeding was said to be congestion of the mucosa of the stomach caused, presumably, by increased venous pressure. Gardner [226] compiled from the literature 22 cases of diaphragmatic hernia with anemia and added 5 others.

A source of incalculable human misery and economic loss is anemia associated with hookworm infestation. It has been variously attributed to toxins produced by the parasite, to derangement of nutrition and to the loss of blood. Suarez [227] in an extensive study of 22 cases of uncinariasis found no interrelation of the hemoglobin content, the number of parasites and the nature of the gastric secretion. He expressed the belief that nutritional factors rather than hemorrhage are of primary importance in causing the anemia. Biggam and Ghalioungui,[228] among others, cured ancylostoma anemia by the administration of iron without preliminary removal of the parasites. Elimination of the worms with-

223. Möller, F.: Zwerchfellhernie und Magenkarzinom: Zugleich einige Betrachtungen über Blutungen und Anämien bei Zwerchfellhernien, Acta med. Scandinav. **74**:421, 1931.

224. Segal, H. L.: Secondary Anemia Associated with Diaphragmatic Hernia, New York State J. Med. **31**:692, 1931.

225. Bock, A. V.; Dulin, J. W., and Brooke, P. A.: Diaphragmatic Hernia and Secondary Anemia; Ten Cases, New England J. Med. **209**:615, 1933.

226. Gardner, K. D.: Diaphragmatic Hernia Associated with Secondary Anemia, Am. J. M. Sc. **185**:561, 1933.

227. Suarez, R. M.: Clinical Aspects of Uncinariasis, Puerto Rico J. Pub. Health & Trop. Med. **8**:229, 1933.

228. Biggam, A. G., and Ghalioungui, P.: Ancylostoma Anemia and Its Treatment by Iron, Lancet **2**:299, 1934.

out further treatment failed to influence the blood values within a reasonable time. Most favorable results in their series of cases were obtained by the use of reduced iron in doses of 2 Gm. three times a day. A definitely slower response was obtained in patients with gastric anacidity. Recovery from anemia was markedly retarded by the administration of reduced iron in smaller quantities, and very little improvement followed the use of ferrous chloride in a dosage of 0.3 Gm. daily. In the treatment of hookworm anemia they found liver, brewers' yeast and desiccated thyroid to be of no value, and they detected no appreciable effect from the use of copper or manganese as adjuncts to iron. They regarded parenteral therapy with ferric ammonium citrate (0.1 Gm. daily) as generally unsatisfactory, although definitely better results were obtained from intramuscular than from intravenous administration. Observations made on dogs artificially infected with Ancylostoma caninum led Foster and Landsberg [229] to ascribe the anemia solely to the effect of loss of blood. They were able to "parallel in every detail the picture of a developing hookworm anemia, including its response to iron therapy, by periodic artificially produced hemorrhage." The extensive investigations of Rhoads, Castle, Payne and Lawson [230] led them to believe that hookworm anemia is due primarily to hemorrhage, which is the sole effect of the parasites per se on the blood, but that a secondary and important rôle is played by dietary deficiency and the gastro-intestinal changes resulting from defective nutrition. They found the anemia characterized by hypochromia and microcytosis with increased cellularity of the bone marrow. Excellent therapeutic results were obtained by the use of ferric ammonium citrate (6 Gm. daily) regardless of the nature of the diet. They suggested that to patients with hookworm infestation without anemia small doses of iron should be given as a prophylactic measure.

To the extensive researches of Whipple, Robscheit-Robbins and their collaborators is due much of the knowledge concerning the effects of prolonged or recurrent hemorrhage in depleting not only the body's iron reserves but other materials required for the synthesis of hemoglobin and the formation of erythrocytes. The Nobel prize lecture of Whipple [231] provides so excellent a summary of their work that no extensive recapitulation seems indicated here. Whipple, Hooper and

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229. Foster, A. O., and Landsberg, J. W.: Nature and Cause of Hookworm Anemia, Am. J. Hyg. **20**:259, 1934.

230. Rhoads, C. P.; Castle, W. B.; Payne, G. C., and Lawson, H. A.: Observations on Etiology and Treatment of Anemia Associated with Hookworm Infestation in Puerto Rico, Medicine **13**:317, 1934.

231. Whipple, G. H.: Hemoglobin Regeneration as Influenced by Diet and Other Factors, J. A. M. A. **104**:791 (March 9) 1935.

Robscheit [232] in 1920 reported the favorable influence of liver on the regeneration of blood in dogs after rapid production of anemia by one or more severe hemorrhages. In 1925 Robscheit-Robbins and Whipple [233] demonstrated the preeminence of liver in terms of the quantitative production of hemoglobin by dogs maintained at a constant level of anemia through repeated removal of small quantities of blood. The results received wide clinical application. With the exception of pernicious anemia, in which the action of liver is that of a specific, there is no unanimity of opinion with regard to the efficacy of liver in the treatment of anemia in human beings. As might be expected, however, its use together with iron has been found of greater value in the management of anemia due to chronic hemorrhage than of others of the iron deficiency group. Keefer and Yang [234] are among the strongest advocates of liver therapy, having found it of greatest benefit in anemia due to chronic hemorrhage, hookworm infestation and faulty diet. Murphy and Powers [235] have reported the value of liver with iron in the treatment of anemia due to hemorrhage, and Dyke [236] and Wahlberg [237] have obtained reticulocyte responses during treatment with liver alone for this type of anemia.

DEFICIENCY ANEMIAS OF INFANCY

Bunge [206] found the mineral contents of human milk and of newborn infants to be quantitatively similar with the exception of iron, in which milk proved to be notably deficient. Consequently, he felt that a prolonged milk diet led to iron deficiency and so caused anemia.

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232. Whipple, G. H.; Hooper, C. W., and Robscheit, F. S.: Blood Regeneration Following Simple Anemia: I. Mixed Diet Reaction, Am. J. Physiol. **53**: 151, 1920; Blood Regeneration Following Simple Anemia: IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets, ibid. **53**: 236, 1920.

233. Robscheit-Robbins, F. S., and Whipple, G. H.: Blood Regeneration in Severe Anemia: Favorable Influence of Liver, Heart and Skeletal Muscle in Diet, Am. J. Physiol. **72**:408, 1925.

234. Keefer, C. S., and Yang, C. S.: Value of Liver and Iron Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929. Yang, C. S., and Keefer, C. S.: Response of the Reticulocytes in Secondary Anemias Following Various Forms of Treatment, Arch. Int. Med. **45**:456 (March) 1930. Keefer, C. S., and Yang, C. S.: Treatment for Secondary Anemia: Study of Results in One Hundred and Twenty-Six Cases, ibid. **48**:537 (Oct.) 1931.

235. Murphy, W. P., and Powers, J. H.: Value of Liver in Treatment of Anemia Due to Hemorrhage, Surg., Gynec. & Obst. **48**:480, 1929. Powers, J. H., and Murphy, W. P.: Treatment of Secondary Anemia: Further Observations, J. A. M. A. **96**:504 (Feb. 14) 1931.

236. Dyke, S. C.: Liver Therapy in Secondary Anemia, Lancet **1**:1192, 1929.

237. Wahlberg, J.: Liver Diet and Reticulocyte Reaction in Simple Anemia, Acta med. Scandinav. **72**:143, 1929.

Hugounenq [238] in 1899 analyzed the ash obtained from incineration of fetuses secured at different periods of gestation. He demonstrated that during the last trimester of pregnancy twice as much iron is stored as is laid down during the preceding six months. In 1917 Lichtenstein [239] recorded the observations and drew the conclusions which today form the basis of the knowledge concerning the commoner type of anemia of infants. Hemoglobin and erythrocyte values in the majority of new-born premature babies he found to agree with those obtained from full-term infants. The stained films of the blood of the former, however, revealed a greater incidence of fetal characteristics. Uniformly, he reported, during the first two months of life there develops in the premature infant an anemia characterized by reduction of both the erythrocyte count and the hemoglobin value. This anemia he called hypoplastic, believing it to be due to the partial failure of the immature blood-forming organs to meet the demands imposed by extra-uterine life. During the second quarter of the first year he found that the erythrocyte count of the premature infant increased, whereas the hemoglobin content remained at a low level. This deficiency in hemoglobin he attributed to an insufficient congenital supply of iron together with a milk diet furnishing inadequate amounts of the metal. Thus, the condition was regarded, at least in part, as an alimentary anemia. The failure of others to obtain results from iron in the treatment of this type of anemia Lichtenstein attributed to the use of too small doses. His patients, treated successfully, were given metallic iron (0.15 Gm. daily) in powdered form mixed with cane sugar.

The recognition of the bearing of nutrition on anemia in infancy and childhood stimulated investigations of the requirement of iron by normal children. Lichtenstein [240] studied during short periods the intake and excretion of iron in premature infants and found a slight positive balance to be the rule. Rose, Vahlteich, Robb and Bloomfield [241] for nine days carried out a careful study of the iron metabolism in a girl 2½ years of age. The average daily intake of iron was 4.64 mg. and the daily output, 5.74 mg., yielding a negative balance of 1.1 mg. For children between 2 and 3 years these investigators advised an iron intake of at least 0.75 mg. for each hundred calories furnished by the diet.

238. Hugounenq, M. L.: Recherches sur la statique des éléments minéraux et particulièrement du fer chez le foetus humain, Compt. rend. Soc. de biol. **51**:337, 1899.

239. Lichtenstein, A.: Hematological Studies of Premature Babies During Infancy with Particular Reference to Anemic Conditions, Svenska läk.-sällsk. handl. **43**:1533, 1917; abstr., Arch. Pediat. **43**:738, 1926.

240. Lichtenstein, A.: Der Eisenumsatz bei Frühgebornenen, Acta pædiat. **1**: 194, 1921.

241. Rose, M. S.; Vahlteich, E. M.; Robb, E. and Bloomfield, E. M.: Iron Requirement in Early Childhood, J. Nutrition **3**:229, 1930.

Wallgren [242] conducted twenty-one studies of the iron balance on 5 nursing infants between 3 weeks and 11 months of age. The duration of each experiment was from seven to ten days. All but 4 showed a slight positive balance. Wallgren concluded that if milk contains as little iron as 0.0642 mg. per hundred cubic centimeters there is still a sufficient supply to meet the external requirements of the healthy nursing infant, as some dependence may be placed on the iron stores present at birth. Snelling [243] performed twelve experiments on balance, lasting from three to six days, on 7 premature infants. The excretion of pigment was also recorded. Tests on 9 infants on a milk diet revealed a positive balance, and 3 gave a slight negative value. Snelling failed to find excessive excretion of pigment and he believed that the anemia, characterized by equivalent reduction of values for both erythrocytes and hemoglobin, was due to failure to utilize available materials rather than to an increased destruction of blood or to a lack of substances required for the composition of hemoglobin. He suggested that this imperfect utilization was "due to inadequate medullary space coincident with the premature cessation of hematopoietic activity in the liver." Josephs [244] conducted studies of balance of from two to six months' duration on 6 normal full-term infants. During the first two months a slightly negative balance occurred, followed by a fairly constant positive balance with an average gain of 6 mg. of iron each month. He concluded that the birth stores of iron are required but rarely for the formation of hemoglobin before the third month, and that under normal conditions they are probably sufficient for this purpose until the end of the sixth month. He stated that a diet exclusively of milk cannot cause any great degree of anemia solely on the basis of its low iron content but that in the production of such anemia other factors causing a disturbance of iron metabolism must play a part. Josephs [245] also studied the blood and the excretion of urobilin of a large group of premature infants. During the first six to eight weeks there was a progressive fall in the blood count, the color index remained high, and the rate of destruction of blood exceeded the rate of growth. In this period there was some, but little, excretion of body iron (negative balance). The greater part of the iron released by the breakdown of hemoglobin was available for new blood, and in premature infants, according to

242. Wallgren, A.: Le fer dans la nutrition de l'enfant: III. Recherches sur le métabolisme du fer chez les enfants nourris au sein pendant la première année de leur existence, Rev. franç. de pédiat. **9**:196, 1933.

243. Snelling, C. E.: Metabolism of Iron in Anemia of Premature Infants, J. Pediat. **2**:546, 1933.

244. Josephs, H. W.: Iron Metabolism in Infancy: Relation to Nutritional Anemia, Bull. Johns Hopkins Hosp. **55**:259, 1934.

245. Josephs, H. W.: Anemia of Prematurity, Am. J. Dis. Child. **48**:1237 (Dec.) 1934.

Josephs, a true iron deficiency or hypochromic anemia does not occur before the fourth or fifth month. Between the sixth to tenth week and the fourth to fifth month a period of hypoplastic anemia is evident in the sense that the blood count continues to fall, with the color index remaining high, but the bone marrow is reactive and a reticulocyte response will follow the administration of either iron or liver. "They act as stimulators of hemopoietic activity." During the subsequent "hypochromic period" iron serves as a building material for hemoglobin, whereas liver, as a rule, is ineffective for this purpose.

For important contributions both to the understanding of iron metabolism and to the therapy of certain types of nutritional anemia workers are indebted to the Wisconsin investigators Hart, Steenbock, Waddell and Elvehjem.[246] They demonstrated that the anemia induced in growing rats by feeding an exclusive milk diet could not be cured by the administration of pure iron salts but that the availability of iron for the formation of hemoglobin depended on the presence of small amounts of copper. Myers and Beard[247] denied the specificity of copper for this purpose and claimed a similar "biological catalytic" action for numerous other metals. Drabkin and Miller[248] found the amino-acids glutamic acid and arginine useful as adjuncts to iron in the treatment of the nutritional anemia of the growing rat. However, it is generally felt that these apparently conflicting results were due to undetected quantities of copper present either in the diet or in the therapeutic agents employed. The unique rôle of copper as an "activator" of iron has been confirmed by numerous investigators including ourselves.

The addition of copper to therapeutic preparations of iron has failed to produce striking results in the treatment of most types of human anemia. Josephs,[249] Lewis[250] and Bloxsom,[251] among others, have found copper a useful adjunct to iron in the treatment of hypochromic anemia of infancy and early childhood, and it appears that copper may achieve a definite place in the therapy of such anemia. Recently Daniels and

246. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Iron in Nutrition: Copper as Supplement to Iron for Hemoglobin Building in Rat, J. Biol. Chem. **77**:797, 1928.

247. Myers, V. C., and Beard, H. H.: Studies in the Nutritional Anemia of the Rat: Influence of Iron Plus Supplements of Other Inorganic Elements upon Blood Regeneration, J. Biol. Chem. **94**:89, 1931.

248. Drabkin, D. L., and Miller, H. K.: Hemoglobin Production: Relief of Anemia Due to Milk Diet by Feeding Amino-Acids, J. Biol. Chem. **90**:531, 1931.

249. Josephs, H.: Treatment of Anemia of Infancy with Iron and Copper, Bull. Johns Hopkins Hosp. **49**:246, 1931.

250. Lewis, M. S.: Iron and Copper in the Treatment of Anemia in Children, J. A. M. A. **96**: 1135 (April 4) 1931.

251. Bloxsom, A. P.: Copper and Iron Requirements in Infancy, South. M. J. **25**: 401, 1932.

Wright [252] reported the results of fifteen studies of the iron and copper balance made on 8 normal children from 4 to 6 years of age. They found an average daily retention of iron of 0.18 mg. per kilogram of body weight and concluded that a diet furnishing 0.6 mg. per kilogram meets the requirements of iron for the maintenance and growth of normal children of the ages studied. The average daily retention of copper from a diet supplying 0.086 mg. per kilogram of body weight was 0.026 mg. per kilogram. The investigators found higher values for retention of copper when greater quantities were ingested and so recommended that the daily diet supply a minimum of 0.1 mg. of copper per kilogram of body weight. It is probable that studies of the requirements of iron and copper in food will have to be reevaluated in the light of recent work on the availability for absorption of the iron and copper contained in various foods.[253]

That the subject of iron deficiency and nutritional anemia in childhood is worthy of the attention accorded it in this review is attested by the work of Mackay [254] in England. In the poorer classes of London she found anemia present in the great majority of artifically fed babies. This she considered to be due primarily to a lack of iron, since the administration of a preparation of the metal to these infants was followed by an increase of the hemoglobin content in 81 per cent. She discovered no relationship between this type of anemia and vitamin deficiency, lack of sunlight or fat toxemia. Ferric ammonium citrate, from 0.3 to 0.6 Gm. daily, mixed with dried milk was used in the treatment of her patients. Parsons and Hawksley [255] obtained a more rapid increase in the hemoglobin content following the administration of 0.8 Gm. of ferrous sulphate daily. Neither they nor Mackay [256] were able to demonstrate the value of adding copper to purified preparations of iron in the treatment of nutritional anemia of infancy. Recently,

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252. Daniels, A. L., and Wright, O. E.: Iron and Copper Retentions in Young Children, J. Nutrition **8**:125, 1934.

253. Sherman, W. C.; Elvehjem, C. A., and Hart, E. B.: Further Studies on the Availability of Iron in Biological Materials, J. Biol. Chem. **107**:383, 1934. Schultze, M. O.; Elvehjem, C. A., and Hart, E. B.: Availability of Copper in Various Compounds as Supplement to Iron in Hemoglobin Formation, ibid. **106**: 735, 1934.

254. Mackay, H. M. M.: Anemia in Infancy: Prevalence and Prevention, Arch. Dis. Childhood **3**:117, 1928; Nutritional Anemia in Infancy: Some Observations on a Common Deficiency Disease, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **22**, 29, 1929.

255. Parsons, L. G., and Hawksley, J. C.: Studies in Anemias of Infancy and Early Childhood: Anhaematopoietic Anemias (Deficiency Diseases of the Erythron); Nutritional Anemia, and Anemias of Prematurity, Scurvy, and Coeliac Disease, Arch. Dis. Childhood **8**:117, 193[2]

256. Mackay, H. M. M.: Copper in the Treatment of Nutritional Anemia in Infancy, Arch. Dis. Childhood **8**: 145, 1933.

Hawksley, Lightwood and Bailey [257] reported 12 cases of associated hypochromic anemia and achlorhydria occurring in infants and children after a test meal with alcohol. The anemia responded well to iron therapy, and they regarded it as probably identical with the simple achlorhydric anemia of adults.

ANEMIA ASSOCIATED WITH PUBERTY

Severe anemia of the hypochromic, microcytic type is occasionally encountered in young girls who have recently passed through adolescence. Such anemia is almost invariably the result of excessive or disordered menstruation dependent on endocrine dysfunction, and its discussion is not within the scope of this review. Chlorosis, formerly the outstanding member of this group of anemias, has so completely vanished from clinical experience that it is mentioned but to be dismissed.

HYPOCHROMIC ANEMIA IN ADULTS RELATED TO DIETARY DEFECTS AND DISORDERS OF DIGESTION

Unless associated with other factors such as loss of blood, pregnancy or impaired absorption from the digestive tract, a diet poor in iron rarely if ever leads to anemia in full grown persons. Lintzel,[258] after conducting experiments on iron balance, each of which lasted about two weeks, found that there was a balance in his subjects while they were receiving a daily intake varying between 0.9 and 63.8 mg. He concluded that the daily requirement for iron for an adult without complications is less than 0.9 mg. A diet furnishing so small a quantity of iron is difficult to devise, and is probably never encountered in practice. Davidson and his collaborators [259] found anemia (hemoglobin content less than 9.66 Gm. per hundred cubic centimeters) in 45 per cent of 455 women, representatives of the poorer classes of Aberdeen. An analysis of many typical diets disclosed a uniformly low iron content, amounting in some instances to a daily supply of less than 6 mg. (A well planned diet supplies a daily intake of from 12 to 20 mg. of iron.) However, gastric achlorhydria or marked hypochlorhydria was found in 89 per cent of these anemic women, and the remainder gave a history of gross loss of blood. Among male members of this social group anemia was not found except for obvious cause. The authors attributed the high

257. Hawksley, J. C.; Lightwood, R., and Bailey, U. M.: Iron Deficiency Anemia in Children: Its Association with Gastro-Intestinal Disease, Achlorhydria, and Haemorrhage, Arch. Dis. Child. **9**: 359, 1934.

258. Lintzel, W.: Zur Frage des Eisenstoffwechsels: über den Eisenbedarf des Menschen, Ztschr. f. Biol. **89**: 342, 1929.

259. Davidson, L. S. P.; Fullerton, H. W.; Howie, J. W.; Croll, J. M.; Orr, J. B., and Godden, W.: Observations on Nutrition in Relation to Anemia, Brit. M. J. **1**:685, 1933.

incidence of anemia among women chiefly to an increased demand for iron dependent on frequent pregnancies or excessive loss of blood during menstruation and at parturition. They were able to effect a rapid cure by the administration of 6 Gm. of ferric ammonium citrate daily. The problem of the bearing of nutrition on the formation of blood is by no means limited to a consideration of iron metabolism. Present knowledge of the dietary factors exerting direct and indirect influence on hematopoiesis as well as the larger question of the relationship between the blood level and the nutritional state of the entire organism has been excellently summarized by Davidson and Leitch.[260]

During recent years increasing interest has been shown in an anemia of women which is not attributable to any single cause. The salient features of this condition are anemia of hypochromic, microcytic type occurring in women during the child-bearing period, persisting for long periods at a more or less constant level, usually associated with achlorhydria or hypochlorhydria and readily responsive to iron therapy, yet showing a strong tendency to recur on discontinuance of medication. To Faber [261] belongs the credit for the recognition of the importance of an anemia characterized by a low color index accompanying achylia gastrica. Kaznelson, Reimann and Weiner [262] provided the first complete description of this form of anemia. In addition to the characteristics listed previously, they mentioned the frequent occurrence of "pains in the bones," burning of the tongue with atrophy of the papillae, menstrual disorders, slight splenomegaly and koilonychia, a concavity of the nails giving them a spoon-shaped appearance. Examination of the sternal marrow of one of their patients revealed a great increase in the number of normoblasts, an observation later confirmed by Witts,[263] Dameshek [264] and Rosenthal and Abel.[265]

Chronic dysphagia associated with anemia was described simultaneously by Kelly [266] and Paterson [267] in 1919. Three years later Vinson [268]

260. Davidson, L. S. P., and Leitch, I.: Nutritional Anemias of Man and Animals, Nutrition Abstr. & Rev. **3**:901, 1934.

261. Faber, K.: Achylia gastrica mit Anämie, Med. Klin. **5**:1310, 1909; Anämische Zustände bei der chronischen Achylia gastrica, Berl. klin. Wchnschr. **50**:958, 1913.

262. Kaznelson, P.; Reimann, F., and Weiner, W.: Achylische Chloranämie, Klin. Wchnschr. **8**:1071, 1929.

263. Witts, L. J.: Achlorhydria and Anemia, Practitioner **124**:348, 1930.

264. Dameshek, W.: Primary Hypochromic Anemia (Erythro-Normoblastic Anemia): New type of Idiopathic Anemia, Am. J. M. Sc. **182**:520, 1931.

265. Rosenthal, N., and Abel, H. A.: Simple Achlorhydric Anemia, Bull. New York Acad. Med. **9**:24, 1933.

266. Kelly, A. B.: Spasm at the Entrance to the Oesophagus, J. Laryng., Rhin. & Otol. **34**:285, 1919.

267. Paterson, D. R.: A Clinical Type of Dysphagia, J. Laryng., Rhin. & Otol. **34**:289, 1919.

268. Vinson, P. P.: Hysterical Dysphagia, Minnesota Med. **5**:107, 1922.

reported 69 cases and stated that Plummer had noted the condition in 1914. Moersch and Conner [269] in 1926 and Witts [270] in 1931 found achlorhydria in the majority of their cases, and this observation has been confirmed by most subsequent investigators, although Cameron [271] reported normal secretion of acid to be the rule in his case. The Plummer-Vinson syndrome, a term commonly applied to the association of functional dysphagia with hypochromic anemia, has been well reviewed by Suzman.[272] He and Wintrobe and Beebe [273] regard this syndrome in no sense as a distinct entity and consider dysphagia merely as an occasional complication of long-standing hypochromic anemia. With this view there is general accord.

A striking similarity may exist between the symptomatology of pernicious anemia and that of hypochromic anemia with achlorhydria. Such resemblance is probably based on the presence in both conditions of gastric anacidity, and its occurrence may be limited to those cases in which the secretory defect is of constitutional or hereditary origin. The gastric secretion of patients with anemia has been well studied by Davies [274] and by Hartfall with Witts.[275] The latter concluded that the important causes of achlorhydria are hereditary traits, gastritis and surgical procedures on the stomach. They described a family in which members of successive generations were found to have pernicious anemia, hypochromic anemia with achlorhydria or achlorhydria without anemia. Similar observations have been made by Gram,[276] Schulten,[277] Hurst [278] and Heath.[279] Hartfall and Witts [280] have demonstrated that

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269. Moersch, H. J., and Conner, H. M.: Hysterical Dysphagia, Arch. Otolaryng. **4**:112 (Aug.) 1926.

270. Witts, L. J.: Syndrome of Glossitis, Dysphagia and Anemia, Guy's Hosp. Rep. **81**:193, 1931.

271. Cameron, M.: Dysphagia and Anaemia, J. Laryng. & Otol. **44**:168, 1929.

272. Suzman, M. M.: Syndrome of Anemia, Glossitis and Dysphagia: Report of Eight Cases, with Special Reference to Observations at Autopsy in One Instance, Arch. Int. Med. **51**:1 (Jan.) 1933.

273. Wintrobe, M. M., and Beebe, R. T.: Idiopathic Hypochromic Anemia, Medicine **12**:187, 1933.

274. Davies, D. T.: Studies on Achlorhydria and Anemia, Quart. J. Med. **24**: 447, 1931.

275. Hartfall, S. J., and Witts, L. J.: Gastric Secretion in Simple Achlorhydric and Allied Anemias, Guy's Hosp. Rep. **8**:3, 1933.

276. Gram, H. C.: A Study of the Development of Pernicious Anemia, Folia haemat. **39**:461, 1930.

277. Schulten, H.: Zur Behandlung hypochromer Anämien mit maximalen Eisendosen, München. med. Wchnschr. **77**:355, 1930.

278. Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connexion with Addison's Anaemia: Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anaemia, Quart. J. Med. **1**:157, 1932.

(Footnotes continued on next page)

the gastric secretion of persons with hypochromic anemia and achlorhydria is not deficient in the intrinsic factor of Castle, but that it may become so is evidenced by the reports of cases in which hypochromic anemia was ultimately replaced by pernicious anemia.[281]

Limitations of space prohibit the discussion of a number of recent significant contributions to the subject of chronic hypochromic anemia.[282] Much additional information will be found in the excellent articles of Witts[283] and Wintrobe and Beebe.[273]

It is our opinion that the anemia under consideration cannot be regarded as a distinct disease. Its general characteristics may be found

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279. Heath, C. W.: Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia: Study of Family in Which Both Conditions Occurred Singly and Combined, Am. J. M. Sc. **185**:365, 1933.

280. Hartfall, S. J., and Witts, L. J.: Intrinsic Factor of Castle in Simple Achlorhydric Anemia, Guy's Hosp. Rep. **83**:24, 1933.

281. (*a*) Witts, L. J.: Varieties of Secondary Anemia and Their Treatment, Lancet **2**:531, 1931. (*b*) Minot, G. R.: Idiopathic Hypochromic Anemia, Libman Anniv. Vols. **2**:831, 1932.

282. (*a*) Reimann, F., and Fritsch, F.: Vergleichende Untersuchungen zur therapeutischen Wirksamkeit der Eisenverbindungen bei den sekundären Anämien, Ztschr. f. klin. Med. **115**:13, 1930. (*b*) Witts, L. J.: Simple Achlorhydric Anaemia, Guy's Hosp. Rep. **80**:253, 1930. (*c*) Reimann, F., and Fritsch, F.: Experimentelle und klinische Untersuchungen über die Wirkung des Ferrum Reductum, Ztschr. f. klin. Med. **117**:304, 1931. (*d*) Mills, E. S.: Idiopathic Hypochronemia, Am. J. M. Sc. **182**:554, 1931. (*e*) McCann, W. S., and Dye, J.: Chlorotic Anemia with Achlorhydria, Splenomegaly and Small Corpuscular Diameter, Ann. Int. Med. **4**:918, 1931. (*f*) Adamson, J. D., and Smith, F. H.: Chronic Chlorosis, Canad. M. A. J. **24**:793, 1931. (*g*) Davies, D. T.: Simple Achlorhydric Anemia, Lancet **2**:385, 1931. (*h*) Waugh, T. R.: Hypochromic Anemia with Achlorhydria, Arch. Int. Med. **47**:71 (Jan.) 1931. (*i*) Baur, M.: Die Pharmakologie des Eisens, Ztschr. f. d. ges. phys. Therap. **43**:89, 1932. (*j*) Beebe, R. T., and Wintrobe, M. M.: Effect on Idiopathic Hypochromic Anemia of Beef Steak (Hamburger Steak) Digested with Normal Gastric Juice, Arch. Int. Med. **52**:464 (Sept.) 1933. (*k*) Alt, H. L.: "Hypoferric" Anemia, Illinois M. J. **64**:72, 1933. (*l*) Wright, C. B.: Chronic Microcytic Anemia: Its Relationship to Menstrual Disturbances and Achlorhydria, Northwest Med. **32**:1, 1933. (*m*) Lundholm, I.: Achylianämi med nagelförändringar och glossit, Svenska läk.-tidning. **30**:244, 1933. (*n*) Mettier, S. R.; Kellogg, F., and Rinehart, J. F.: Chronic Idiopathic Hypochromic Anemia. Etiologic Relationship of Achlorhydria to Anemia, with Special Reference to the Effect of Large Doses of Iron, Organic (Dietary) Iron, and of Predigested Food upon Formation of Erythrocytes, Am. J. M. Sc. **186**:694, 1933. (*o*) Weber, F. P., and Weisswange, W.: Simple Achlorhydric Anemia in Adult Males, Brit. M. J. **2**:1066, 1933. (*p*) Burgher, G. N., and Witts, L. J.: Hypochromic Anemia in Men, Guy's Hosp. Rep. **84**:14, 1934. (*q*) Vaisey, A. W.: Additional Symptomatology in Simple Achlorhydric Anemia, Brit. M. J. **1**:143, 1934. (*r*) Meulengracht, E.: Simple Achylic Anemia After Gastro-Enterostomy and Partial Gastrectomy, Acta med. Scandinav. **81**:87, 1934. (*s*) Schur, M.: Ueber Eisenmangelanämien, Wien. Arch. f. inn. Med. **25**: 321, 1934. Footnotes 264 and 281*b*.

283. Witts, L. J.: Chronic Microcytic Anemia, Brit. M. J. **2**:883, 1931.

in any case of anemia due solely to chronic hemorrhage of long duration, whereas its specific features are limited to those cases exhibiting achlorhydria and are probably the result of complex secretory dysfunction of the stomach. Mettier and Minot [284] have claimed more effective utilization of iron for the production of hemoglobin from its administration in an acid than in an alkaline medium, and the studies of Reimann and Fritsch [285] yielded substantial evidence that the acidity of the gastric contents has a definite bearing on the absorption of iron. The majority of persons with achlorhydria do not have anemia, yet it is possible that in the presence of anacidity such extensive alterations may occur throughout the digestive tract that insufficient iron is absorbed to supply the needs for maintenance. It seems more probable, in view of the practical restriction of this type of anemia to the female sex, that other factors, such as repeated pregnancy or excessive menstruation, play contributory rôles. The work of Fowler and Barer [286] indicated that menorrhagia may be far more common than is generally supposed. Those authors found that the menstrual loss could be increased from five to twenty times the normal amount without recognition of any abnormality by the patient. Although the term "idiopathic hypochromic anemia" bestows an unwarranted individuality on the condition and implies that nothing is known of its etiology, it is probably less objectionable than other designations suggested for this type of anemia. "Simple achlorhydric anemia" and "achylic chloranemia" are unsuitable, since gastric anacidity is not a prerequisite for this type of anemia. "Chronic chlorosis" is inappropriate as there is little clinical similarity between this condition and that designated as chlorosis.

The treatment of idiopathic hypochromic anemia involves the elimination, when possible, of those factors which may contribute to its causation. Such measures include correction of deficient diet, attention to sources of hemorrhage, avoidance of frequent pregnancy and attempts to improve the gastric secretion by the treatment of gastritis and the removal of septic foci.[260] Meulengracht [213] and Faber and Gram [287] were among the first to emphasize the value of large doses of preparations of iron in the treatment of this form of anemia. Their observations have been widely confirmed. Although simple ferrous compounds would seem to merit preference, in practice reduced iron and the com-

284. Mettier, S. R., and Minot, G. R.: Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931.

285. Footnotes 282 *a* and *c*.

286. Fowler, W. M., and Barer, A. P.: Iron Retention Following Use of Ferric Ammonium Citrate in Hypochromic Anemia, J. A. M. A. **104**: 144 (Jan. 12) 1935.

287. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch. Int. Med. **34**:658 (Nov.) 1924.

plex scale preparations, such as ferric ammonium citrate, in adequate dosage are equally efficacious. Mills,[282d] Adamson and Smith[282f] and Dameshek[288] have advised the administration of small quantitites of copper (from 5 to 15 mg. daily) as an adjunct to iron in the therapy of idiopathic hypochromic anemia. Giffin and Watkins,[289] Heath,[290] Rosenthal and Abel[265] and we[291] have denied its value. Other materials suggested for their possible beneficial effect on hematopoiesis in this type of anemia are a powdered extract of fetal calves' liver,[292] concentrated bile pigment[293] and a "pernicious anemia fraction" liver extract for parenteral administration.[294]

DEFINITE DISEASE ENTITIES OF THE BLOOD

POLYCYTHEMIA

Etiology.—Polycythemia associated with a marasmic bodily state develops in rats on a salt-poor ration with casein as the protein provided that a constant weight following a period of subnormal growth has been maintained for at least fifty-six days.[295] Injections of cobalt chloride subcutaneously produce polycythemia in frogs, mice and guinea-pigs.[296] An increase in the total cell volume has been produced by feeding cobalt to rats.[297] It does not develop if the spleen is removed.[298]

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288. Dameshek, W.: Primary Hypochromic Anemia: Clinical Features, J. A. M. A. **100**:540 (Feb. 25) 1933.

289. Giffin, H. Z., and Watkins, C. H.: Treatment of Secondary Anemia, J. A. M. A. **95**:587 (Aug. 23) 1930.

290. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**: 459 (March) 1933.

291. Bethell, F. H.; Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Diagnosis and Treatment of the Iron-Deficiency Anemias, J. A. M. A. **103**:797 (Sept. 15) 1934.

292. Berglund, H.; Watkins, C. H., and Johnson, R.: Rapid Stimulation of Hemoglobin Synthesis in Secondary Anemias After Feeding Fetal Calf's Liver, Proc. Soc. Exper. Biol. & Med. **25**:814, 1928.

293. Patek, A. J., Jr., and Minot, G. R.: Bile Pigment and Hemoglobin Regeneration: Effect of Bile Pigment in Cases of Chronic Hypochromic Anemia, Am. J. M. Sc. **188**:206, 1934.

294. Murphy, W. P.: Treatment of Secondary Anemia, with Special Reference to Use of Liver Extract Intramuscularly, Arch. Int. Med. **51**:656 (May) 1933.

295. Swanson, P. P., and Smith, A. H.: Inorganic Salts in Nutrition; Changes Induced in Blood by Ration Deficient in Inorganic Constituents, J. Biol. Chem. **98**: 479, 1932; Inorganic Salts in Nutrition: Progressive Changes in Blood of Rats Maintained upon Ration Poor in Inorganic Salts, ibid. **98**:499, 1932.

296. Sutter, Jean: Cobalt et hyperglobulie, Compt. rend. Soc. de biol. **116**: 994, 1934.

297. Orten, J. M.; Underhill, F. A.; Mugrage, E. R., and Lewis, R. C.: Polycythemia in Rat on Milk-Iron-Copper Diet Supplemented by Cobalt, J. Biol. Chem. **96**:11, 1932.

298. Berwald, W. P. E.; Arseneau, J. H., and Dooley, M. S.: Effect of Cobalt Sulphate on Erythrocyte Count of Splenectomized Albino Rat, Proc. Soc. Exper. Biol. & Med. **32**:430, 1934.

A familial, congenital type involving three brothers, a paternal uncle and two of his sons has been reported.[299] The term "benign familial polycythemia" has been suggested to cover the nonsymptomatic polycythemia (with polyglobulia and splenomegaly) present in 7 members of a family.[300]

Among the various theories as to the cause of polycythemia data in support of the following have been published recently: It may be a clinical expression of chronic anoxemia with subsequent stimulation of the bone marrow as a result.[301] The anoxemia may be a local factor in the bone marrow because of subintimal and adventitial fibrosis in the arteries and arterioles of the marrow.[302] On testing the theory that polycythemia is due to an anoxemic stimulus, it was found that 2 patients living for two weeks in an oxygen tent (50 per cent oxygen) showed no significant change in the red blood cell count. Cramplike pains, however, were relieved during the treatment.[303] Data for the neoplastic nature of the disease have been presented.[304] Others have considered that the secretion of too much of the intrinsic factor of Castle causes an increased production of red blood cells.[305] Polycythemia may be present with achylia gastrica.[306] Polyglobulia may be associated with certain tuberopituitary syndromes, with the production of a normal red blood cell count after removal of the pituitary tumor.[307] An elevated erythrocyte count may accompany generalized tuberculosis with involve-

299. Mussio-Fournier, J. C., and Lussich Siri, J. J.: Forme congénitale de la polycythémie idiopathique familiale, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:121, 1933.

300. Spodaro, A., and Forkner, C. E.: Benign Familial Polycythemia, Arch. Int. Med. **52**: 593 (Oct.) 1933. Wieland, E.: Weitere Untersuchungen über Polycythaemia Vera im Kindesalter, Ztschr. f. Kinderh. **53**:703, 1932.

301. Waring, J. J., and Yegge, W. B.: Polycythemia in Association with Pulmonary Disorders, Ann. Int. Med. **7**:190, 1933.

302. Reznikoff, P.; Foot, N. C.; Bethea, J. M., and DuBois, E. F.: Racial and Geographic Origin of Patients Suffering from Polycythemia Vera and Pathological Findings in Blood Vessels of Bone Marrow, Tr. A. Am. Physicians **49**:273, 1934.

303. Barach, A. L., and McAlpin, K. R.: Negative Results of Oxygen Therapy in Polycythemia Vera, Am. J. M. Sc. **185**:178, 1933.

304. Weber, F. P.: Erythemia, Proc. Roy. Soc. Med. **26**: 362, 1933.

305. Morris, R. S.; Schiff, L., and Foulger, M.: Erythremia (Polycythemia Vera) Theory Regarding Etiology, J. Med. **13**:318, 1932.

306. Michaelides, F.: Ueber einen Fall von Polycythaemia vera und Achylia gastrica, Wien. klin. Wchnschr. **45**: 1250, 1932.

307. Guillain, G.; Lechelle, P., and Garcin, R.: La polyglobulie, avec ou sans erythrose, de certains syndromes hypophysotubériens: (Retour à la normale du nombre des globules rouges après exérèse chirurgicale d'une tumeur hypophysaire), Ann. de méd. **31**:100, 1932. Moehlig, R. C., and Bates, G. S.: Influence of Pituitary Gland on Erythrocyte Formation, Arch. Int. Med. **51**:207 (Feb.) 1933. Baserga, A.: Poliglobulie da lesioni diencefalo-ipofisarie, Policlinico (sez. med.) **41**:17, 1934.

ment of the spleen.[308] Polycythemia caused by epinephrine is inhibited by the injection of yohimbin.[309] Venesection and roentgen irradiation over the long bones do not cause an increase in the production of reticulocytes such as follows treatment with phenylhydrazine.[310]

Treatment.—Treatment with phenylhydrazine hydrochloride may be continued for long periods, and some patients have been able to discontinue the drug entirely after from two to four years of treatment.[311] Acetylphenylhydrazine has some advantages over phenylhydrazine hydrochloride (decreased toxicity, more easily regulated dosage and greater margin of safety).[312] Roentgen irradiation in comparatively small doses over many parts of the body besides the long bones at two to four day intervals produced a remission in 1 patient.[313] Others have produced remissions by intensive treatments over the long bones.[314] In a patient who did not respond to roentgen therapy, small doses of phenylhydrazine (0.01 Gm.) twice weekly gave a satisfactory remission without toxic symptoms.[315] The erythrocyte count may be reduced with the administration of n-propyl disulphide.[316] Raw onion has also been used.[317]

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308. Heymann, K. G., and Bussel, R.: Ueber Polyglobulie bei generalisierter Tuberculose und ihre Beziehung zur Milz, Jahrb. f. Kinderh. **136**:26, 1932. Margolis, A., and Warszawski, S.: Case of Tuberculous Splenomegaly with Polycythemia, Polska gaz. lek. **12**:645, 1933.

309. Simoes-Raposo, L.; Fevereiro, A., and Leite, S.: Mécanisme de l'érythrocytose: Polyglobulie adrénalinique et hypoglobulie yohimbinique, Compt. rend. Soc. de biol. **109**:1044, 1932.

310. Falconer, E. H.: Treatment of Polycythemia: Reticulocyte Response to Venesection, Phenylhydrazin and Radiation, Ann. Int. Med. **7**:172, 1933.

311. Giffin, H. Z., and Allen, E. V.: The Control and Complete Remission of Polycythemia Vera Following the Prolonged Administration of Phenylhydrazin Hydrochlorid, Am. J. M. Sc. **185**:1, 1933. Stealy, C. L.: Polycythemia Vera: Report of Case Treated with Phenylhydrazine Hydrochloride Over a Period of Seven and One Half Years, J. A. M. A. **98**:1714 (May 14) 1932. McAlpin, K. R., and Edsall, K. S.: Polycythemia Vera: Report of Ten Cases Treated with Phenylhydrazine, New York State J. Med. **33**:1039, 1933.

312. Stone, C. T.; Harris, T. H., and Bodansky, M.: Treatment of Polycythemia Vera: Report of Two Cases, J. A. M. A. **101**:495 (Aug. 12) 1933.

313. Chambers, W. E.: Polycythemia Vera, M. Bull. Vet. Admin. **9**:428, 1933.

314. de Meyer, J., and Sluys, F.: Deux cas de maladie de Vaquez (polycythemia rubra vera) traités par la roentgenthérapie de la moelle osseuse, Scalpel **85**:259, 1932. Rossoni, R.: Contributo al trattamento radioterapico del m. di Vaquez, Radiol. med. **19**:156, 1932. Sgalitzer, M. Röntgenallgemeinbestrahlung bei Polyglobulie, Fortschr. a. d. geb. d. Röntgenstrahlen **46**:90, 1932.

315. Hare, D. C.: Splenomegalic Polycythemia Treated with Minimal Doses of Phenylhydrazine, Proc. Roy. Soc. Med. **26**:363, 1933.

316. Sharp, E. A.; Vonderheide, E. C., and McKean, R. M.: Beneficial Effect of N-Propyl Disulphide in Polycythemia Vera: Case Report, J. Michigan M. Soc. **31**:394, 1932.

317. Boissannas, L.: Un cas de maladie de Vaquez traité avec succès par l'oignon cru, Rev. franç. de pédiat. **8**:745, 1932.

After the administration of phenylhydrazine there is a temporary negative nitrogen balance (increased excretion of urea, proteinuria, decreased intake of nitrogen). The total consumption of oxygen is parallel to the endogenous nitrogen catabolism. The liberated iron is retained by the body.[318] Urea and bilirubin are formed more rapidly than they are excreted. The phosphorus balance is approximately maintained. Leukocytosis and reticulocytosis are features. There is a decrease in the viscosity of the blood.[318a]

Symptoms.—Ménière's vertigo may accompany the polycythemia.[319] Necrosis of the extremities may be a complication.[320]

Prognosis.—The disease may terminate in anemia. [321] A remission of eleven years, with subsequent relapse, has been noted.[322]

PURPURA HAEMORRHAGICA

Purpura may result from many causes, and various forms have been classified under different headings. A review of the literature shows multiple classifications; all of them are complex,[323] and their clinical value is somewhat doubtful. The three factors which determine the bleeding are: (*a*) the platelets, (*b*) the permeability of the capillaries and (*c*) the blood plasma. It is thought that the diminution in the number of platelets is due either to their deficient formation in the bone marrow or to their increased destruction by the reticulo-endothelial system (primarily the spleen). Some authors are of the opinion that the decreased number of platelets is the result of hemorrhage rather than the cause, the thrombocytes being withdrawn from the circulation and fixed in the bleeding areas as a defense mechanism.[324]

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318. (*a*) Barer, A.; Paul, W. D., and Baldridge, C. W.: Studies in Relationships Between Oxygen Consumption and Nitrogen Metabolism: III. In Polycythemia Vera, J. Clin. Investigation **13**:15, 1934. (*b*) Reznikoff, P.: Iron Metabolism Studies, ibid. **11**:807, 1932.

319. Bieling, K.: Ménièrescher Schwindel bei Polyzythämie, Med. Klin. **29**: 1410, 1933. Koch, J., and Rothmann, H.: Ménièreartige Erscheinungen bei Polyzythämie, ibid. **29**:320, 1933.

320. Klieneberger, C.: Erfrierungseinwirkung als Unfall im Sinne von Verschlimmerung, anerkannt bei Gefässverschlüssen der Erythraemia vera, Monatschr. f. Unfallh. **40**:276, 1933. Becker, F.: Extremitätennekrose bei Polycythaemia Vera, Klin. Wchnschr. **11**:1260, 1932.

321. Platt, R.: Case of Polycythaemia Rubra Developing Anaemia, Brit. M. J. **1**:750, 1932.

322. Falconer, E. H.: An Unusual Remission in Polycythemia Vera, J. A. M. A. **101**:1633 (Nov. 18) 1933.

323. Wyllie, W. G., and Ellis, R. W. B.: Clinical Interpretation of Some Haemorrhagic States, Arch. Dis. Childhood **6**:313, 1931.

324. Rolleston, Humphrey: The History of Hematology, Proc. Roy. Soc. Med. **27**: 1161, 1934.

Thrombocytopenic purpura may be hereditary or acquired. Often the etiology is not known. It is usually associated with diseases of the bone marrow and spleen or is the result of infection or drugs. Alterations in the permeability of the vascular membranes associated with purpura may be the result of food deficiency, allergy, infection and toxins.[325] It is absolutely necessary to determine the cause of purpura before instituting treatment, and as this cannot always be done many failures of therapy result.

Although splenectomy has often been associated with remarkable improvement, it likewise has proved of no benefit.[326] If the platelets are being destroyed in excessive numbers by the spleen, its surgical removal is indicated; however, it is of little value to perform a splenectomy if the decreased number of platelets is the result of a failure of formation in the bone marrow. It must also be remembered that the operation itself is associated with a high mortality rate. Because of the latter fact, ligation of the splenic artery has been recommended as a substitute for splenectomy.[326a] Foci of infection should always be removed,[327] as well as the source of any toxic substances. Hemorrhagic infectious diseases are often improved by the administration of calcium salts or gelatin intravenously.[326f]

Purpura associated with food deficiency may be alleviated by a well balanced diet especially rich in vitamins and having a high protein and fat content.[326f] Thromboplastic agents have been recommended to aid clotting, and although their efficacy has been proved in vitro there are little if any clinical data to support the laboratory observations.[328] A similar situation exists with radium.[329] Both cures and

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325. Kugelmass, I. N.: Management of Hemorrhagic Problems in Infancy and Childhood, Tr. Sect. Pediat., A. M. A., 1932, p. 147; New York State J. Med. **33**:434, 1933.

326. (*a*) Pemberton, J. deJ.: The Diagnosis and Treatment of Purpura Hemorrhagica, Am. J. Surg. **24**:793, 1934. (*b*) Vastola, A. P.: Acute Thrombocytopenic Purpura Hemorrhagica and Its Treatment, M. J. & Rec. **133**:603, 1931. (*c*) Fagge, H.: Essential Thrombocytopenia with Delayed Response to Splenectomy, Guy's Hosp. Rep. **84**:72, 1934. (*d*) Kracke, R. R.: Effect of Splenectomy in Purpuric Diseases, South. Surgeon **2**:203, 1933. (*e*) Eliason, E. L., and Ferguson, L. K.: Splenectomy in Purpura Hemorrhagica, Ann. Surg. **96**: 801, 1932. (*f*) Kugelmass, I. N.: Management of Hemorrhagic Problems in Infancy and Childhood, J. A. M. A. **99**:895 (Sept. 10) 1932. (*g*) Jones, H. W., and Tocantins, L.: The Treatment of Purpura Hemorrhagica, ibid. **100**:83 (Jan. 14) 1933.

327. Footnotes 326*a* and *g*.

328. Hoffmann, S. S.: Treatment of Henoch's Purpura with Haemoplastin, J. M. A. South Africa **5**: 600, 1931. Gold, H.: Control of Hemorrhage by Thromboplastic Agents, Internat. Clin. **2**:293, 1932.

329. Hoffman, J. M.: Radium in Treatment of Diseases with Subcutaneous or Mucous Membrane Hemorrhages; Preliminary Report, Radiology **14**:136, 1930.

failures have been reported with the administration of liver.[330] Snake venom[331] has become the most recent fad, but there are insufficient data at present to estimate its true clinical worth. A conservative attitude must be adopted concerning the value of the various therapeutic agents recommended, as it must be kept in mind that a spontaneous cure is not uncommon.

HEMOPHILIA

Although the Talmud has a reference to hemophilia, the first clear description of the disease was made in 1803 by Otto. This disease occurs in males and is transmitted by females. Persons with hemophilia usually have more daughters than sons, whereas transmitters have more sons than daughters. Approximately 71 per cent of transmitters' sons have hemophilia; less than 10 per cent of transmitters' daughters have normal sons and from 3 to 7 per cent of daughters of a hemophiliac parent have normal sons.[332]

The diagnosis of hemophilia is based on the following findings: heredity, its occurrence in males, a history of repeated hemorrhages, prolonged clotting time and a normal bleeding time.[333] A study of the elements of the blood reveals a low prothrombin and a high antithrombin content with a slow rate of disintegration of the platelets.[334] Some authors have expressed the belief that the disease is due to faulty development of the liver while others are of the opinion that it is caused by an endocrine deficiency.[335]

Although various types of therapy have been employed, there is no specific treatment for the malady. Some of the more common agents are: whole blood, citrated blood, human plasma, human serum, defibrinated blood, horse serum, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and a special dietary regimen. The therapy may be divided into two stages: prophylactic and treatment of the immediate hemorrhage.

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330. Jacob, F. H., and Clapperton, T.: Cure of Thrombopenic Purpura by Liver, Brit. M. J. **1**:823, 1930. Witts, L. J.: Inefficacy of Liver Treatment in Essential Thrombopenia, Lancet **1**:809, 1931.

331. Stockton, M. R., and Franklin, G. C. H.: Antivenin Therapeusis in Purpura: Case Report, J. A. M. A. **96**:677 (Feb. 28) 1931. Taylor, K. P. A.: Antivenin in Thrombocytopenic Hemorrhage: Importance of Bothropic Type, Am. J. Surg. **21**:285, 1933.

332. Birch, C. L.: Hemophilia, J. A. M. A. **99**:1566 (Nov. 5) 1932.

333. Kugelmass, I. N.: Diagnosis and Management of Hemophilia in Childhood, New York State J. Med. **32**:660, 1932.

334. Kugelmass, I. N.: Mechanism of Hemophilia in Infancy and in Childhood, Am. J. Dis. Child. **44**:50 (July) 1932.

335. Mills, C. A.: Hemophilia, J. Lab. & Clin. Med. **17**:932, 1932.

As a result of recent experimental work [336] it has been stated that the urine of persons with hemophilia does not contain the female sex hormone; however, all authors do not agree with this.[337] Based on this theory of endocrine deficiency, whole ovary and ovarian extracts have been administered to prevent episodes of bleeding. The results have been variable.[338] Tissue extracts [339] and ultraviolet rays [340] likewise have been of little value. Some authors are of the opinion that a diet high in vitamins and protein increases the coagulation time.[341] Saliva has aided coagulation of blood in vitro,[342] but its clinical value has not been demonstrated. Sensitization with animal serum [343] still remains the most satisfactory form of prophylactic therapy.

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336. Birch, C. L.: Hemophilia and Female Sex Hormone (in Urine): Preliminary Report, J. A. M. A. **97**:244 (July 25) 1931. Footnote 334.

337. Brown, R. L., and Albright, F.: Estrin Therapy in Case of Hemophilia, New England J. Med. **209**:630, 1933. Chew, W. V.; Stetson, R. P.; Smith, G. Van S., and Smith, O. W.: Estrogenic, Luteal and Gonadotropic Hormones in Hemophilia, Arch. Int. Med. **55**:431 (March) 1935.

338. Birch, C. L.: Hemophilia (Platelet Study and Treatment with Ovarian Extract and Transplantation), Proc. Soc. Exper. Biol. & Med. **28**:752, 1931. Foord, A. G., and Dysart, B. R.: Treatment of Hemophilia by Ovarian Extract by Birch's Method, J. A. M. A. **98**:1444 (April 23) 1932. Kimm, H. T., and Van Allen, C. M.: Hemophilia: Prevention and Treatment of Bleeding with Ovarian Extract, ibid. **99**:991 (Sept. 17) 1932. Freeman, E. T.: Notes on Hemophilia with Recent Experiments on Clotting Time and Their Influence on Treatment (Ovarian), Irish J. M. Sc. 1933, p. 122. Stetson, R. P.; Forkner, C. E.; Chew, W. B., and Rich, M. L.: The Negative Effect of Prolonged Administration of Ovarian Substance in Hemophilia, J. A. M. A. **102**:1122 (April 7) 1934. Blalock, A.: Amputation of Arm of Patient with Hemophilia, ibid. **99**:1777 (Nov. 19) 1932. Brem, J., and Leopold, J. S.: Ovarian Therapy: Relationship of the Female Sex Hormone to Hemophilia, ibid. **102**:200 (Jan. 20) 1934. Spoto, J. S.: Treatment of Hemophilia with Ovarian Extract; Report of Two Cases, J. Florida M. A. **20**:9, 1933. Hirst, J. C.: The Influence of Female Sex Hormones upon Blood Coagulation of the Newborn, Am. J. Obst. & Gynec. **26**:217, 1933. White, C. E.: Treatment of Hemophilia with Theelin, J. Oklahoma M. A. **25**:304, 1932. Footnotes *332* and *336*.

339. Burns, E. L.; Scharles, F. H., and Aitken, L. F.: Effect of Mixtures of Tissue Extracts and Blood Sera of Various Animals on Coagulation of Blood, Am. J. Physiol. **97**:233, 1931.

340. Sanford, H. N.; Gasteyer, T. H., and Wyatt, L.: Substances Involved in Coagulation of Blood of New-Born: Effect of Ultraviolet Radiation and Viosterol (Irradiated Ergosterol), Am. J. Dis. Child. **43**:566 (March) 1932. Phillips, R. A.; Robertson, D. F.; Corson, W. C., and Irwin, G. F.: Effect of Irradiated Ergosterol on Thrombocytes and Coagulation, Ann. Int. Med. **4**:1134, 1931.

341. Kugelmass, I. N., and Samuel, E. L.: Avitaminosis and Blood Clotting Function, Am. J. Dis. Child. **43**:52 (Jan.) 1932; Dietary Protein and Blood Clotting Function, ibid. **41**:48 (Jan.) 1931.

342. Bellis, C. J.; Birnbaum, W., and Scott, F. H.: Coagulation—Effect of Saliva, Proc. Soc. Exper. Biol. & Med. **29**:1107, 1932.

343. Eley, R. C., and Clifford, S. H.: Hemophilia: Treatment by Protein Sensitization, Am. J. Dis. Child. **42**:1331 (Dec.) 1931. Footnote 333.

Acute hemorrhages are best treated by compression, repeated injection of whole blood into the buttocks, multiple transfusions and administration of epinephrine.[344]

LYMPHOGRANULOMA: HODGKIN'S DISEASE

Numerous reports of cases emphasize the occurrence of lesions in the bones, stomach, spleen, liver, spinal cord (with compression symptoms), mediastinum (with mediastinal pleurisy), skin, tonsils, sternum, thyroid and subdural space. Cases in which tuberculosis, ileus and the symptoms of gastric ulcer were associated with the disease are recorded.

From a study of 108 collected cases of Hodgkin's disease in children, Smith [345] concluded:

1. Hodgkin's disease shows an even greater tendency to attack the male sex in childhood than in other age periods. Over four fifths (81.5 per cent) of 108 collected childhood cases were in boys. In the author's 23 cases, 91.1 per cent were in boys. There is also a marked predominance of the male sex in childhood cases of leucemia and lymphosarcoma.

2. The onset of Hodgkin's disease in childhood showed no significant relationship to preceding illness or to foci of infection, in 23 cases studied. A familial predisposition to the disease is sometimes seen.

3. Secondary invasion with tuberculosis is fairly frequently observed in children with Hodgkin's disease, and the two diseases may coexist for years in the same patient. There is a marked tendency for the tuberculin test to remain negative in the presence of Hodgkin's disease, both in children and in adults. The disease may cause tuberculin anergy.

4. In none of 5 children with Hodgkin's disease tested with avian tuberculin was there a positive reaction.

5. Results of tuberculin tests are not satisfactory evidence as to an etiologic relationship between the two diseases.

6. The histopathology as well as the sex ratios of Hodgkin's disease in childhood are suggestive of a neoplastic rather than a granulomatous process.

7. In childhood the left cervical region is considerably more frequently invaded early than the right, which may be evidence that the disease often has an unsuspected abdominal onset. Invasion of mediastinal glands is common, and often not apparent without x-ray examination. Splenic and hepatic involvement is common late in the disease and is of bad prognostic import. Cutaneous manifestations are comparatively infrequent in childhood.

8. Septic and recurrent relapsing (Pel-Ebstein) temperatures are not rare in children with Hodgkin's disease, and are bad prognostic signs.

9. Blood studies of 20 children with Hodgkin's disease showed a progressive anemia, and a tendency to leucopenia and to an increase in monocytes.

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344. Pereira, H., and Pereira, A.: Treatment of Haemophilic Diseases by Whole Blood, Brit. M. J. **1**:283, 1930. Kugelmass, I. N.: Clinical Control of Chronic Hemorrhagic States in Childhood, J. A. M. A. **102**:287 (Jan 27) 1934. Footnote 335.

345. Smith, C. A.: Hodgkin's Disease in Childhood: Clinical Study with Résumé of Literature to Date, J. Pediat. **4**:12, 1934.

10. Though fulminating, rapidly fatal Hodgkin's disease is common in childhood, the average duration of 16 fatal cases was 3.45 years. Five living patients have survived an average of 4.2 years. The average duration of 41 fatal cases from the literature was 1.8 year. Cases beginning in childhood and now alive twelve and fifteen years after onset have been seen in this clinic.

11. The use of roentgen irradiation is recommended, though absolute proof of its ultimate benefit cannot be adduced from our cases. A program for its use is suggested.

As to duration and prognosis Craver [346] found:

Of 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3 per cent showed a survival following irradiation of 5 years or over—of the proven cases, 12 per cent. Five year survivors averaged 10 years younger (34 years of age) than a group that had survived 6 months or less, though extremes of age were the same in the two groups. The difference in survival of the two groups is apparently due to difference in virulence of the disease. This, however, showed no correlation with the histologic appearance of nodes removed at biopsy. Favorable features were localization in one area, combined with early thorough treatment, absence of leukocytosis or leukopenia, gain in weight after irradiation. Fever, marked pruritis and splenomegaly were apparently unfavorable signs.

Leucutia,[347] in an analysis of 2,425 collected cases, found that 30 per cent of the patients with lymphosarcoma survived for five years and from 10 to 15 per cent for ten years. In the remaining groups, the expectation of life has been increased by adequate treatment from two and one-half to three and one-twelfth years.

In Hodgkin's disease, the 5 year survival reaches 15 per cent to 33 per cent, but the cases in the great majority remain carriers of the disease, necessitating frequent resumption of irradiation. A ten year survival or cure occurs in 8 per cent of the cases or less. In those who died within the first 5 years, the average expectancy of life was increased from 2 to 3½ years. The symptomatic improvement is nearly always marked but not so spectacular as in lymphosarcoma.

Different workers recommend varying dosages of roentgen ray. McAlpin and Golden [348] recommended small doses at frequent intervals, and Levitt [349] mentioned doses "considerably below the tolerance of the skin and healthy tissues," and considered that the so-called roentgen ray bath (generalized exposures of the trunk and abdomen to repeated small doses) has great possibilities.

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346. Craver, Lloyd F.: Five-Year Survival in Hodgkin's Disease, Am. J. M. Sc. **188**:609, 1934.

347. Leucutia, T.: Irradiation in Lymphosarcoma, Hodgkin's Disease and Leukemia (a Statistical Analysis), Am. J. M. Sc. **188**:612, 1934.

348. McAlpin, K. R., and Golden, Ross: Roentgen Treatment of Lymphoblastoma (Hodgkin's Disease), Am. J. Roentgenol. **29**:83, 1933.

349. Gordon, M. H.; Gow, A. E.; Levitt, W. M., and Weber, F. P.: Recent Advances in the Pathology and Treatment of Lymphadenoma, Proc. Roy. Soc. Med. **27**:1035, 1934.

Of 172 patients with Hodgkin's disease, 27 were found to have involvement of the bones. The vertebrae and pelvis are most frequently affected. Osteoplastic and osteolytic changes with collapse of the vertebrae occur. For treatment, Heublein's method of prolonged continuous low intensity irradiation of the entire body has been recommended. For the gross lesions of the bones, single large erythema doses or fractional doses of high voltage roentgen rays are used by some. After treatment relief from pain and healing processes in the bones have been noted.[350]

Gordon's test [351] for Hodgkin's disease consists in the inoculation of the material from lymph nodes into the brains of rabbits. With material from a patient with true Hodgkin's disease a paralysis of the hindlegs with ataxia is produced, whereas the results are negative when normal lymphatic tissue is used, or lymphosarcoma, leukemia or tuberculous tissue, bacteria, sterile milk peptone, and albuminoid substance and lecithin sodium nucleinate, quinine, ethyl carbamate (urethane) or powdered glass. Of 5 patients with Hodgkin's disease 3 gave a positive reaction, 1 a doubtful reaction and 1 a negative reaction.[351a]

Avian tubercle bacilli were found in 6 of 8 cases of Hodgkin's disease. It was not possible to infect rabbits, guinea-pigs, pigeons or chickens by intravenous, intraperitoneal or intramuscular injection.[352] Steiner [353] was unable to detect avian tubercle bacilli in tissue from 15 patients with Hodgkin's disease, and he was not able to transmit the disease to animals by the injection of glandular material. Gordon [349] had similar results.

On the basis that Hodgkin's disease may be caused by avian tuberculosis, chicken serum has been given experimentally with conclusive results.[354] Specific vaccines have so far been ineffective.[349] Infection has been suggested as a predisposing factor to lymphoblastoma.[355] Krumbhaar [356] favors the theory of infection rather than one of neoplastic origin of Hodgkin's disease, but Weber [349] considers it as having a "neoplastic trend."

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350. Craver, L. F., and Copeland, M. M.: Changes in the Bone in Hodgkin's Granuloma, Arch. Surg. **28**:1062 (June) 1934.

351. (*a*) Van Rooyen, C. E.: A Biological Test in the Diagnosis of Hodgkin's Disease, Brit. M. J. **1**:644, 1933. (*b*) Footnote 349.

352. Van Rooyen, C. E.: Aetiology of Hodgkin's Disease with Special Reference to B. Tuberculosis Avis, Brit. M. J. **1**:50, 1933.

353. Steiner, P. E.: Hodgkin's Disease: Search for Infective Agent and Attempts at Experimental Reproduction, Arch. Path. **17**:749 (June) 1934.

354. Barrett, N. R., and Bond, L. T.: Serum Treatment of Hodgkin's Disease with Account of Four Cases Treated, Lancet **2**:855, 1933. Pulvertaft, R. J. V.: Treatment of Lymphadenoma with Chicken Serum, ibid. **2**:857, 1933.

355. Desjardins, A. U.: The Etiology of Lymphoblastoma, J. A. M. A. **103**: 1033 (Oct. 6) 1934.

356. Krumbhaar, E. B.: Is Typical Hodgkin's Disease Infection or Neoplasm? Am. J. M. Sc. **188**:597, 1934.

LEUKEMIA

Types and Incidence.—During the past few years increased prominence has been given to monocytic leukemia, at least 56 cases having been reported during a three year period.[357] It is possible that many cases of this type were formerly considered as instances of atypical myelogenous leukemia. Many of the cases reported as being "monocytic" were of other types, so that it is not possible to estimate the relative incidence of the disease with any degree of accuracy. In most of the cases reported the course has been fairly acute, and the condition has not been influenced favorably by roentgen therapy.

Among other unusual types of leukemia reported are eosinophilic,[358] megakaryoblastic[359] and plasma cell leukemia.[360] Cases of leukemia have been reported from Italy, Russia, Germany, England, Poland, Spain, France, the United States, Japan, The Netherlands, Chile and other countries, suggesting a world-wide incidence. Leukemia-like conditions have been reported in dogs, mice and fowl. A case of myelogenous leukemia has been reported in a 5 week old infant.[361] The occurrence of leukemia in two brothers has been noted.[362]

Etiology.—A leukemia-like picture has been produced in mice by the weekly injection of benzene in olive oil,[363] and cases in human beings

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357. Doan, C. A., and Wiseman, B. K.: The Monocyte, Monocytosis, and Monocytic Leukosis: Clinical and Pathological Study, Ann. Int. Med. **8**:383, 1934. Clough, P. W.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **51**:148, 1932. Forkner, C. E.: Clinical and Pathologic Differentiation of Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, Arch. Int. Med. **53**:1 (Jan.) 1934. Farrar, G. E., and Cameron, J. D.: Monocytic Leukemia with Data on the Individuality and Development of the Monocyte, Am. J. M. Sc. **184**:763, 1932. Levine, V.: Monocytic Leukemia: Report of Nine Cases, Folia haemat. **52**:305, 1934.

358. McCowen, G. R.; Parker, H. B., and Panton, P. N.: Case of Acute Eosinophilic Leukemia, J. Roy. Nav. M. Serv. **18**:131, 1932.

359. von Boros, J., and Korenyi, A.: Ueber einen Fall von akuter Megakaryoblastenleukemie, zugleich einige Bemerkangen zum Problem der akuten Leukämie, Ztschr. f. klin. Med. **118**:697, 1931.

360. Muller, G. L., and McNaughton, E.: Multiple Myeloma (Plasmatocytomata) with Blood Picture of Plasma Cell Leukemia: Report of Two Cases, Folia haemat. **46**:17, 1931.

361. Giblin, J.: Case of Myelogenous Leukemia Occurring in Infant Five Weeks Old, Arch. Pediat. **50**:662, 1933.

362. Petri, Sven: Ueber familiäres Auftreten der Leukämie, Acta path. et microbiol. Scandinav. **10**:330, 1933.

363. Lignac, G. O. E.: Benzolleukämie bei Menschen und weissen Mäusen, Klin. Wchnschr. **12**:109, 1933; comment by Teleky, ibid. **12**:472, 1933.

have been reported.[364] Malaria was described as a predisposing factor in 1 case[365] and nonfilarial elephantiasis in another.[366]

Lymphatic leukemia may be transmitted in certain strains of mice by inoculation of material derived from mice with spontaneous leukemia.[367] Efforts to separate the active agent from the cells in the material used for inoculation have not been successful, as in the case of the leukemia-like condition in chickens.[368]

Pathology.—Abnormalities in the mitotic division of leukocytes of myelogenous leukemia, nonspecific but resembling the condition in cancer, have been noted in tissue cultures.[369] The dividing leukoblasts may show only half the somatic number of chromosomes,[370] and the "mitosis angle" may differ from normal.[371] The elevated basal metabolic rate may be associated with the disturbance in thyroid function from leukemic invasion.[372] Metastatic calcification of the endocardium, pulmonary veins, aorta and main pulmonary artery, lungs and kidneys has been noted, with calcium mobilized from the long bones.[373] Localized tumors (myeloblastic sarcoma) have been observed during the course of the

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364. Falconer, E. H.: Instance of Lymphatic Leukemia Following Benzol Poisoning, Am. J. M. Sc. **186**:353, 1933. Weil, P. E.: La leucémie post-benzolique, Bull. méd., Paris **46**:750, 1932.

365. Reynolds, F. H.: Case of Lymphatic Leukaemia, Indian M. Gaz. **68**:84, 1933.

366. Larrabee, R. C., and Peers, J. H.: A Case of Nonfilarial Elephantiasis Terminating with Aleukemoid Anemia, J. A. M. A. **102**:1936 (June 9) 1934.

367. Richter, M. N., and MacDowell, E. C.: Studies on Mouse Leukemia; Relation of Cell Death to Potency of Inoculated Cell Suspensions, J. Exper. Med. **57**:1, 1933.

368. Feldman, W. H., and Olson, C.: The Pathology of Spontaneous Leukosis of Chickens, J. Am. Vet. M. A. **82**:875, 1933. Furth, J.: Lymphomatosis, Myelomatosis and Endothelioma of Chickens Caused by Filterable Agent; Transmission Experiments, J. Exper. Med. **58**:253, 1933; Studies on Nature of Agent Transmitting Leucosis of Fowls; Resistance to Desiccation, to Glycerin, to Freezing and Thawing; Survival at Ice Box and Incubator Temperatures, ibid. **55**:495, 1932; Studies on Nature of Agent Transmitting Leucosis in Fowls: Its Concentration in Blood Cells and Plasma and Relation to Incubation Period, ibid. **55**:465, 1932; Immunity Phenomena in Transmissable Leucosis of Fowl, Proc. Soc. Exper. Biol. & Med. **29**:1236, 1932.

369. Andres, A. H., and Shiwago, P. I.: Karyologische Studien und myeloischer Leukämie des Menschen, Folia haemat. **49**:1, 1933.

370. Groat, W. A.: Leukemias Showing Haploid Leukoblasts Undergoing Mitotic Division in Circulating Blood, Am. J. M. Sc. **185**:624, 1933.

371. Hittmair, A.: Ueber Mitosenwinkelmessung, Folia haemat. **47**:230, 1932.

372. Friedgood, H. B.: Relation of Sympathetic Nervous System and Generalized Lymphoid Hyperplasia to Pathogenesis of Exophthalmic Goiter and Chronic Lymphatic Leukemia, Am. J. M. Sc. **183**:841, 1932.

373. De Santo, D. A.: Metastatic Calcification Occurring in Myelogenous Leukemia, Am. J. Path. **9**:105, 1933.

disease.[374] From studies of sections of bone marrow Jaffé [375] concluded that the anemia which occurs in chronic myelogenous leukemia is due not to the replacement of the erythropoietic tissues but to excessive destruction of red cells (hemosiderosis). The same author noted the presence of active tuberculosis in 3 of 30 cases of chronic myelogenous leukemia. In none of these was there any evidence that the leukemic cells (myeloblasts) took part in the defense against the infection.[376] Lymphosarcoma may terminate with a leukemic blood picture.[377] Leukemic infiltration of the bones with periosteal thickening, cortical erosion and medullary rarefaction has been noted.[378] Aleukemic myelosis may be associated with osteosclerosis and fibrosis of the bone marrow and splenomegaly.[379]

Symptomatology.—A variation in symptoms has been the feature in reports of cases: no enlargement of the spleen or lymph nodes;[380] cutaneous infiltrates[381] with changes in the nasal mucosa; coexistence with tuberculous adenitis; miliary tuberculosis; isolated symmetrical

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374. Dubois, F. S.: Myeloblastic Sarcoma of Scapula Associated with Chronic Splenomyelogenous Leukemia, Am. J. Path. **9**:113, 1933.

375. Jaffé, R. H.: Morphology of Inflammatory Defense Reactions in Leukemia, Arch. Path. **14**:177 (Aug.) 1932; Erythropoiesis in Leukemia, Folia haemat. **49**:51, 1933.

376. Jaffé, R. H.: Tuberculosis and Leukemia, Am. Rev. Tuberc. **27**:32, 1933.

377. Kato, K., and Brunschwig, A.: Acute Leukemia Following Lymphosarcoma, Arch. Int. Med. **51**:77 (Jan.) 1933.

378. Smith, C. H.: Leukopenic Myeloid Leukemia Associated with Arthritis, Am. J. Dis. Child. **45**:123 (Jan.) 1933. Poynton, F. J., and Lightwood, R. C.: Lymphatic Leukaemia, with Infiltration of Periosteum Simulating Acute Rheumatism, Lancet **1**:1192, 1932. Ehrlich, J. C., and Forer, S.: Periosteal Ossification in Myelogenous Leukemia: Report of Case Associated with Acute Rheumatic Fever, Arch. Int. Med. **53**:938 (June) 1934. Snelling, Charles E., and Brown, Alan: Bone Changes in Leukemia; Clinical and Roentgenological, Arch. Dis. Childhood **9**:315, 1934.

379. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087, 1932.

380. Hirschfeld, H.: Ueber chronische Leukämien ohne Milz- und Lymphknotenvergrösserung, Med. Klin. **28**:1160, 1932.

381. Jordan, A., and Schamschin, W.: Hautveränderungen bei aleukämischer Lymphadenose, Dermat. Ztschr. **66**:1, 1933. MacKenna, R. M. B., and Davie, T. B.: Lymphatic Leukaemia with Cutaneous Manifestations, Lancet **1**:1196, 1932. Artz, L.: Leukämische Erkrankungen der Haut, Wien. klin. Wchnschr. **46**:1125, 1933. Bykowa, O.: Retikulo-endotheliale Leukosen (Mit Affektion der Haut), Folia haemat. **51**:96, 1933. Frank, T. J. F.: Case of Acute Lymphatic Leuchaemia with Leuchaemia Cutis and Leucimides, M. J. Australia **1**:126, 1934. Hollander, L.; Kastlin, G. J.; Permar, H. H., and Schmitt, C. L.: Myeloid Leukemia with Cutaneous Manifestations, Arch. Dermat. & Syph. **29**:821 (June) 1934. Sydenstricker, V. P., and Phinizy, T. B.: Acute Monocytic Leukemia; A Case with Partial Autopsy, Am. J. M. Sc. **184**:770, 1932.

aleukemic lymphadenosis of the orbit; orbital tumor;[382] labyrinthine lesion with acute otitis media and mastoiditis; mediastinal tumor, causing deafness; herpes zoster,[383] exophthalmos;[384] acute appendicitis with rupture;[385] a condition simulating appendicitis; ascites,[386] and aphonia.[387] Leukemic infiltrations and hemorrhages in the central nervous system may cause symptoms such as bilateral facial paralysis[388] and papilledema.[389] Stomatitis after the extraction of a tooth may be the first intimation of the presence of the disease.[390]

In the absence of a blood picture suggesting leukemia, Baldridge and Barer[391] suggested the following criteria for aleukemic myelosis:

1. Severe unexplained anemia with a color index of about 1 and with a moderate increase in reticulocytes.
2. Hemorrhagic purpura which does not respond to transfusions of blood.
3. Tumefaction of the gums.
4. Unexplained enlargement of the spleen or lymph nodes.
5. Symptoms of arthritis without selective atrophy of the muscles, increased tendon reflexes or palpable changes in the joints.
6. Painful nerve roots or deep bony pain.
7. Lytic lesions in bones (for example, lesions of the ribs seen in a roentgenogram of the chest).

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382. Cohen, M.: Orbital Lymphoma in Chronic Lymphatic Leukemia: Report of Case, Arch. Ophth. **11**:617 (April) 1934.

383. Haack, K.: Zoster Generalisatus bei lymphatischer Leukämie, Dermat. Wchnschr. **95**:1819, 1932. Craver, L. F., and Haagensen, C. D.: Note on Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma and Leukemias, Am. J. Cancer **16**:502, 1932.

384. Reese, A. B., and Guy, L.: Exophthalmos in Leukemia, Am. J. Ophth. **16**:718, 1933.

385. Rose, B. H.: Acute Ruptured Appendicitis Complicating Chronic Leukaemic Myelosis, New York State J. Med. **33**:195, 1933.

386. Cheney, G.: Chronic Myelogenous Leukemia with Ascites Resembling Banti's Syndrome: With Report of Two Cases, Acta med. Scandinav. **81**:14, 1934.

387. Stinson, W. D.: Aphonia in Acute Leukemia, J. Tennessee M. A. **27**:33, 1934.

388. Garvey, P. H., and Lawrence, J. S.: Facial Diplegia in Lymphatic Leukemia, J. A. M. A. **101**:1941 (Dec. 16) 1933. Howell, A., and Gough, J.: Acute Lymphatic Leukaemia with Facial Diplegia and Double Abducens Palsy, Lancet **1**:723, 1932.

389. Hill, E.: Papilledema and Intracranial Complications of Leukemia, Am. J. Ophth. **15**:1127, 1932. Hawksley, J. C.: Lymphocytic Leukaemia Causing Pontine Haemorrhage, Arch. Dis. Childhood **7**:29, 1932. Olmer, J., and Alliez, J.: Les complications medullaires des leucémies, Presse méd. **40**:1986, 1932.

390. Sergeant and Laugier: Stomatite après avulsion dentaire; Signe révélateur d'une leucémie aigüe, Rev. de stomatol. **35**:1, 1933.

391. Baldridge, C. W., and Barer, A.: Relationship Between Oxygen Consumption and Nitrogen Metabolism In Leukemia, Arch. Int. Med. **51**:589 (April) 1933.

8. Leukopenia with a shift to the left in an afebrile patient.
9. Erythroblasts found unexpectedly in a smear.
10. Pathologic fractures.
11. High consumption of oxygen in a patient without fever or exophthalmic goiter.
12. Unexplained acute enlargement of the breasts or ovaries.

Of less moment are the following manifestations:

1. Reddish-gray, nonliquefied tissue discovered at operation for osteomyelitis.
2. Priapism.
3. Abnormally high value for plasma globulin or fibrinogen.
4. Unexplained hypercalcemia or hypocholesteremia.
5. Bence-Jones' proteinuria.
6. Abnormally rapid rouleau formation (Reimann).
7. Unexplained anticomplementary Wassermann tests.

Blood.—In 45 per cent of the cases of acute leukemia there may be a total count of less than 10,000 cells per cubic millimeter. The presence of blast and immature cells is essential in the diagnosis of leukemia of the leukopenic type (aleukemic leukemia).[392] Heterophile agglutinins are confined to low titers, less than 1 to 4, serving as a differential feature from infectious mononucleosis.[393] The blood proteose is increased in chronic myelogenous leukemia and in acute leukemia, with variations in different stages of the diseases.[394] In tissue cultures of leukemic blood myeloblasts may develop into myelocytes, but the evidence that myelocytes mature into polymorphonuclear leukocytes or that erythrocytes mature from the more primitive forms is not definite.[395] The consumption of oxygen and glycolytic activity of leukocytes in normal and leukemic blood in vitro have been reported as inversely proportional to the concentration of the white blood cells[396] as opposed to previously reported observations that mature polymorphonuclear cells consume more oxygen under these conditions than the immature forms.

Treatment.—A remission of six months after radium treatment and splenectomy has been reported in a case of myelogenous leukemia.[397]

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392. Watkins, C. H.: Acute Leukopenic Leukemia and Its Differential Diagnosis, Wisconsin M. J. **32**:156, 1933.

393. Bernstein, A.: Diagnostic Importance of the Heterophile Anti-Body Test in Leukemia, J. Clin. Investigation **13**:677, 1934.

394. Cooke, J. V.: Proteolytic Leukocytic Enzyme in Leukemia; Study Made by Quantitative Method, Arch. Int. Med. **49**:836 (May) 1932.

395. Pierce, M.: Cultures of Leukemic Blood Leukocytes, Arch. Path. **14**:295 (Sept.) 1932.

396. Soffer, L. J., and Wintrobe, M. M.: The Metabolism of Leucocytes from Normal and Leukemic Blood, J. Clin. Investigation **11**:661, 1932.

397. Carling, E. R.; Carlill, H., and Pulvertaft, R. J. V.: Splenectomy in Myeloid Leukaemia, Proc. Roy. Soc. Med. **26**:373, 1933.

A remission of sixteen years following radiotherapy is recorded.[398] Among the types of treatment, Jenkinson[399] suggested short wave irradiation over the anterior and posterior parts of the chest. The entire spleen is not irradiated. A soft spleen, even though enlarged, gives good results from treatment, but fever and a low hemoglobin content are unfavorable. Phillips[400] reported good results from the use of a 4 Gm. radium bomb. Roentgen therapy does not cure the disease but may increase the efficiency of the patient at least 60 per cent.[401] Different authors have recommended concentrated,[402] protracted[401] or small[403] treatments, depending on whether they considered that the roentgen rays cause cells to mature and die of senility[402b] or kill them in the stage in which they are irradiated. A case has been reported[404] of aleukemic lymphatic leukemia in which there was a high basal metabolic rate and in which an induction of a symptomatic and hematopoietic remission followed thyroidectomy. Symptomatic improvement in a case of chronic lymphatic leukemia may follow the use of compound solution of iodine, with a decrease in the symptoms associated with an elevated basal metabolic rate.[405] Among other types of treatment reported are teleroentgenotherapy,[406] sulphur pyretotherapy, total irradiation[407] and lead therapy (leukosis in chickens).[408] The resump-

398. Fiessinger, N., and Arnaudet, A.: Leucémie lymphoide à forme splénique pure en excellent état après 16 ans de traitement, Sang **6**:411, 1932.

399. Jenkinson, E. L.: Myelogenous Leucemia, Am. J. Roentgenol. **29**:91, 1933.

400. Phillips, G. W.: Myeloid Leukaemia Treated with the Four-Gramme Radium Bomb, Lancet **1**:22, 1933.

401. Leucutia, T.: Irradiation in Lymphosarcoma, Hodgkin's Disease and Leukemia: Statistical Analysis, Am. J. M. Sc. **188**:612, 1934.

402. Isaacs, R.: (*a*) Present Status of Study and Treatment of Leucemia, J. Lab. & Clin. Med. **17**:1006, 1932; (*b*) Maturing Effect of Roentgen Rays on Blood-Forming Cells, Arch. Int. Med. **50**:836 (Dec.) 1932.

403. Orton, G. H.: Importance of Small Dosage in X-Ray Treatment of Leukaemia, Brit. J. Radiol. **6**:242, 1933.

404. Dameshek, W.; Berlin, D. D., and Blumgart, H. L.: Complete Ablation of Thyroid Gland in Case of Chronic Lymphatic Leukemia with Hypermetabolism, New England J. Med. **210**:723, 1934.

405. Friedgood, H. B.: Effect of Lugol's Solution on Chronic Lymphatic Leukemia and Its Bearing upon Pathogenesis of Exophthalmic Goiter, Am. J. M. Sc. **183**:515, 1932.

406. Marchal, G., and Mallet, L.: Sur une nouvelle méthode de radiothérapie dans le traitement des leucémies: La téléroentgenthérapie totale, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:737, 1933.

407. Ebbehoj, K.: Total Roentgen Irradiation in Therapy of Leukemias, Hospitalstid. **76**:445, 1933.

408. Zadik, P.: Erfolgreiche Behandlung der Hühnerleukose mit Blei. (Ein Versuch die Tumornatur der Hühnerleukose ex juventute abzuleiten), Folia haemat. **50**:460, 1933.

tion of the use of solution of potassium arsenite is recommended.[409] Some authors recommend interruption of pregnancy in leukemic patients,[410] although a normal baby may be born. Transfusion of blood may produce a temporary remission, especially in a case of acute leukemia.[411] Radiothorium alone or in combination with roentgen rays has been advocated.[412] In susceptible persons the blood count may be influenced by amidopyrine.[413]

Of the different stages of cell growth, the myelocytes and small lymphocytes appear most "sensitive" to roentgenotherapy because when these are the predominant cells in the blood stream irradiation reduces the blood count most effectively. This may be interpreted, however, as not meaning sensitivity but merely indicating that the roentgen rays make a cell go through the next normal stage in its development. The myelocytes mature into polymorphonuclear neutrophils, and the lymphocytes are excreted or destroyed as mature cells. On the other hand, primitive blast cells divide more rapidly, filling the blood-forming organs and ultimately causing death of the patient.[414]

XANTHOMATOSIS AND NIEMANN-PICK'S, SCHÜLLER-CHRISTIAN'S AND GAUCHER'S DISEASES

A very complete study of the anomalies of lipid metabolism (essential primary xanthomatosis, Niemann-Pick's disease, Schuller-

409. Forkner, C. E.: Administration of Solution of Potassium Arsenite in Treatment of Chronic Myelogenous Leukemia, M. Clin. North America **15**: 1057, 1932.

410. Hofstein, J.: La leucémie comme indication d'interruption de la grossesse, Strasbourg med. **91**:611, 1931; Gynéc. et obst. **25**:45, 1932. Kaplan, I. I., and Connery, J. E.: Pregnancy in Course of Leukemia: Case Report, Am. J. M. Sc. **183**:209, 1932. Neumann, H. O.: Die myeloische Leukämie als Indikation zur Schwangerschaftsverhütung, Deutsche med. Wschnschr. **58**:292, 1932. Russell, H. K.: Lymphatic Leucemia and Pregnancy, Am. J. Obst. & Gynec. **25**:493, 1933.

411. Weil, P. E., and Isch-Wall, P.: Un cas de leucémie lymphatique a poussée aigüe avec anémie hyperchrome grave arrêteé par les transfusions sanguines, Sang **7**:204, 1933.

412. Zadek, I.: Radiothorium bei leukämischer Myelose (kleine Dosierungen), Folia haemat. **50**:161 and 369, 1933; **51**:1, 1933; Radiothorium bei leukämischer Myelose: Grosse Dosierungen, ibid. **49**:115, 1933; Tierexperimentelle Ergebnisse mit dem zur Behandlung der Leukämie verwendeten Radiothorium Reinjektionen, Kombinationen mit Röntgenstrahlen, ibid. **48**:279, 1932.

413. (*a*) Terry, M. C., and Sanders, A. O.: A Case of Myeloid Leukemia Treated with Luminal and Amidopyrine, Proc. Soc. Exper. Biol. & Med. **31**: 1154, 1934. (*b*) Isaacs, R.: Relation of Cell Types in Leukemia to Sensitivity to Radiation, Folia haemat. **52**:414, 1934.

414. Footnotes 402 *b* and 413 *b*.

Christian's disease and Gaucher's disease) has been made by Rowland,[415] and others.[416]

AGRANULOCYTOSIS

In November 1922 Schultz [417] described what he considered to be a new clinical syndrome, which he called agranulocytosis. The characteristics of this condition as described by him were ulcerative angina, marked reduction in or disappearance of the granulocytes from the peripheral blood, extreme prostration and frequently a rapidly fatal course. In the following year Friedemann [418] first applied the name agranulocytic angina to the condition. In addition to these names, other terms, such as granulopenia, granulocytopenia, malignant neutropenia and malignant leukopenia, have been introduced. The first case in the United States that was recognized as representing a distinct clinical entity, which was reported under the name of agranulocytic angina, is credited to Lovett,[419] whose report appeared in November 1924. In 1902, twenty-two years before, however, Brown reported a case [420] with observations on the blood which appeared to be an example of this syndrome.

Since the report of Schultz and especially in the past few years the condition appears to be increasing in frequency. Roberts and Kracke [421] stated that it has been reported in many countries throughout the world. The greatest incidence appears to be in Germany and the United States. These observers summarized reports of over 400 cases in the former country and of 473 cases in the latter. It is exceedingly difficult to estimate the true incidence of the disease, first, because an unknown number of cases are not recognized owing to the lack of an examination of the blood and, second, because all cases in which there is marked leukopenia cannot be classified as instances of true

415. Rowland, R. S.: Anomalies of Lipid Metabolism (Constitutional Pathologic Lipoidosis), in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1931, vol. 4, chap. 7 A, 214 (3) and 214 (109) Oct. 1, 1931.

416. Knox, R. A., and Ramsey, G. W.: Niemann-Pick's Disease (Essential Lipoid Histiocytosis), Ann. Int. Med. **6**:218, 1932. Pick, Ludwig: Niemann-Pick's Disease and Other Forms of So-Called Xanthomatosis (Durham Lecture), Am. J. M. Sc. **185**:601, 1933.

417. Schultz, W.: Ueber eigenartige Halserkrankungen (a) Monozytenangina, (b) Gangräneszierende Prozesse und Defekt des Granulozytensystems, Deutsche med. Wchnschr. **48**:1495, 1922.

418. Friedemann, V.: Ueber Angina Agranulocytotica, Med. Klin. **19**:357, 1923.

419. Lovett, B. R.: Agranulocytic Angina, J. A. M. A. **83**:1498 (Nov. 8) 1924.

420. Brown, P. K.: A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leucopenia, Am. Med. **3**:649, 1902.

421. Roberts, S. R., and Kracke, R. R.: Further Studies on Granulopenia with a Report of Twelve Cases, Ann. Int. Med. **8**:129, 1934.

agranulocytosis. For example, Doan [422] stated that only 20 per cent of the patients with leukopenia referred to his clinic have true agranulocytosis.

It should be emphasized that extreme leukopenia may occur secondary to sepsis in cases of various diseases of the blood, such as aplastic anemia, aleukemic leukemia and pernicious anemia, and in certain cases following the therapeutic use of arsenic and gold preparations and after exposure to benzene. Leukopenia which occurs in association with any of the foregoing conditions cannot be regarded as true agranulocytosis but, as Fitz-Hugh and Comroe [423] stated, is a "mere hematological manifestation" of some other disease.

Roberts and Kracke [421] described a mild form of chronic granulopenia which occurs commonly in women between the ages of 40 and 60 years. They stated that the patients have vague complaints such as weakness, exhaustion and fatigue. It is difficult to state what relationship, if any, this condition has to true agranulocytosis, if it is granted that the former syndrome does occur.

In referring to agranulocytosis of the Schultz type, Jackson and Parker [424] concluded that the "hematological picture, clinical course and pathological findings probably entitle it to a consideration as an entity." This appears to express adequately the opinion of a great majority of observers who have studied the condition.

Etiology.—Roberts and Kracke [421] have presented a logical theory concerning the mechanism of the production of the disease, as follows: First, there is the onset in the bone marrow with a failure of myelocytic function. This may be due to myelocytic aplasia or cessation of maturation (maturation arrest). The latter view is held by Fitz-Hugh and Krumbhaar.[425] Second, after a few days there is an onset in the blood stream with a gradual diminution of the granulocytes until the number is greatly reduced or they completely disappear. Third, there is the clinical onset, with the appearance of the characteristic symptoms. Fourth, with a loss of protection, bacterial invasion begins. Fifth, recovery or death follows.

The initial cause of the failure of the bone marrow to produce granulocytes is not clearly understood. It has been held by Brogsitter,[426]

422. Doan, C. A.: Studies on Etiology and Treatment of Neutropenic States, J. A. M. A. **101**:2074 (Dec. 23) 1933.

423. Fitz-Hugh, T., Jr., and Comroe, B. I.: Agranulocytic Angina (Pernicious Leukopenia), Am. J. M. Sc. **185**:552, 1933.

424. Jackson, H., Jr., and Parker, F., Jr.: Agranulocytosis: Its Etiology and Treatment, New England J. Med. **212**:137, 1935.

425. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am. J. M. Sc. **183**:104, 1932.

426. Brogsitter, A. M., and von Kress, H.: Ueber die "Agranulocytose": Krankheit: Eine Kritik der Kasuistik und eigene klinische Beobachtungen, Virchows Arch. f. path. Anat. **276**:768, 1930.

Lovett [419] and many others that the condition was due to severe sepsis. It is now thought that the sepsis is secondary to the condition rather than the primary cause of it.[427] It has been suggested that the initial cause is allergic; [428] others consider that it is an endocrine disturbance.[429] Recently it has been emphasized that the disease may be due to the administration of some therapeutic agent to a person who is susceptible to its action. Granulocytopenia has been observed following the use of arsphenamine and gold salts.[430] Kracke [431] emphasized that certain coal tar drugs may be of importance in the production of the disease, and more recently di-nitrophenol has been reported as an apparent cause of the condition.[432]

An important contribution bearing on the etiology of agranulocytosis was made by Madison and Squier [433] who, in October 1933, reported before the Central Society of Clinical Research certain observations which indicated that amidopyrine might precipitate the syndrome in certain susceptible persons. They reported [434] cases in 14 persons who had taken amidopyrine immediately before the onset of the disease.

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427. Jackson, H., Jr.: Agranulocytic Angina and Allied Conditions, Internat. Clin. **3**:68, 1933. Footnote 421.

428. Pepper, O. H. P.: Leucopenia: A Review with Special Reference to Agranulocytic Angina, California & West. Med. **35**:173, 1931.

429. Baldridge, C. W., and Needles, R. J.: Idiopathic Neutropenia, Am. J. M. Sc. **181**:533, 1931. Thompson, W. P.: Observations on the Possible Relation Between Agranulocytosis and Menstruation with Further Studies on a Case of Cyclic Neutropenia, New England J. Med. **210**:176, 1934. Hubble, D.: Influence of Endocrine System in Blood Disorders, Lancet **2**:113, 1933.

430. Achard, C.; Coste, F., and Cahen, R.: A propos des désordres hématologiques provoqués par les sels d'or, Bull. et mém. Soc. méd. d. hôp. de Paris **48**: 547, 1932. Ameuille and Braillon: Sept cas de syndromes agranulocytaires auriques, ibid. **48**:1627, 1932. Angéras and Ginsbourg: Aleucie hémorragique (agranulocytose) post-chrysothérapique, Sang **6**:798, 1932.

431. Kracke, R. R.: Experimental Production of Agranulocytosis, Am. J. Clin. Path. **2**:11, 1932. Kracke, R. R., and Parker, F. P.: The Etiology of Granulopenia (Agranulocytosis) with Particular Reference to Drugs Containing the Benzene Ring, J. Lab. & Clin. Med. **19**:799, 1934.

432. Bohn, S. S.: Agranulocytic Angina Following the Ingestion of Dinitrophenol, J. A. M. A. **103**:249 (July 28) 1934. Davidson, E. N., and Shapiro, M.: Neutropenia Following Dinitrophenol, with Improvement After Pentnucleotide Therapy and Leukocyte Cream, ibid. **103**:480 (Aug. 18) 1934. Dameshek, W., and Gargill, S. L.: Studies in Agranulocytosis: Report of Two Cases of Agranulocytosis Following Use of Dinitrophenol, New England J. Med. **211**: 440, 1934. Silver, S.: New Danger in Dinitrophenol Therapy: Agranulocytosis with Fatal Outcome, J. A. M. A. **103**:1058 (Oct. 6) 1934.

433. Madison, F. W., and Squier, T. L.: Primary Granulocytopenia After Administration of Benzene Chain Derivatives, J. A. M. A. **101**:2076 (Dec. 23) 1933.

434. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**:755 (March 10) 1934.

Their observations have been confirmed by Watkins,[435] Randall,[436] Hoffman and his associates,[437] Sturgis and Isaacs [438] and others. The fact that a person ingests a certain drug immediately before the onset of a disease is suggestive but not conclusive evidence that it is the cause of the condition. The strongest evidence in support of this view is that Madison and Squier, Sturgis and Isaacs and Plum [439] produced leukopenia in patients who had recovered from agranulocytosis promptly after small doses of amidopyrine were administered. The relationship between amidopyrine and agranulocytosis has been studied by the Council on Pharmacy and Chemistry of the American Medical Association [440] with the conclusion that there is "no question that amidopyrine is very important in the production of granulocytopenia." Plum [439] has reviewed comprehensively the relation of amidopyrine to this condition and states that since May 1933, 128 cases have been reported in which agranulocytosis developed after therapeutic doses of amidopyrine. It should be emphasized, however, that it is not the sole cause of the condition, as Seeman [441] and Jackson [442] have reported a group of cases in which there was definitely no history of such therapy. It is possible that in some of the cases in which the patient reported that he had not taken amidopyrine as such, he may have taken it in combination with a barbiturate or some other drug under a trade name which gave no indication as to the nature of the medication.

Observations on the Blood.—No attempt will be made to discuss the complete blood picture of the disease. It is sufficient to say that the most striking characteristic is a marked reduction or complete disappearance of the granulocytes from the peripheral blood. As the disease progresses the total leukocyte count may be as low as 300 per cubic

435. Watkins, C. H.: The Possible Rôle of Barbiturates and Amidopyrin in Causation of Leucopenic States, Proc. Staff Meet., Mayo Clin. **8**:713, 1933.

436. Randall, Clyde L.: Severe Granulopenia Following the Use of Barbiturates and Amidopyrine: Report of Case, J. A. M. A. **102**:1137 (April 7) 1934.

437. Hoffman, A. M.; Butt, E. M., and Hickey, N. G.: Neutropenia Following Amidopyrine, Preliminary Report, J. A. M. A. **102**:1213 (April 14) 1934.

438. Sturgis, C. C., and Isaacs, R.: Observations Concerning the Etiology of Agranulocytosis, Tr. A. Am. Physicians **46**:328, 1934.

439. Plum, P.: Agranulocytosis Due to Amidopyrine, Lancet **1**:14, 1935.

440. Reznikoff, P.: The Relation of Amidopyrine and the Barbituric Acid Derivatives to Granulocytopenia, Special Report to the Council on Pharmacy and Chemistry of the American Medical Association, J. A. M. A. **102**:2183 (June 30) 1934. This article contains a bibliography on the relation of amidopyrine to agranulocytosis.

441. Seeman, H.: Amidopyrine as Etiological Factor in Agranulocytosis, Ugesk. f. læger **96**:241, 1934.

442. Jackson, H., Jr.: Relation of Amidopyrine and Allied Drugs to Etiology of Agranulocytic Angina, Am. J. M. Sc. **188**:482, 1934.

millimeter, which indicates that in addition to the granulocytes the lymphocytes and monocytes are diminished. An important point with regard to the blood is that in agranulocytosis there is rarely, if ever, a significant degree of anemia. When this is present it usually indicates that the leukopenia is associated with some other disease.[424]

A controversial point in regard to the blood picture concerns the blood platelets. A majority of observers [443] agree that the number of platelets is normal during the acute attack and is often increased as improvement begins. On the other hand, others [444] believe that the number is reduced. Kracke and Roberts [421] stressed that a hemorrhagic tendency is common in the disease, whereas most observers [445] have stated that this finding is rare.

Treatment.—Therapeutic indication in this disease is obviously to increase the number of granulocytes in the peripheral blood, and various measures have been introduced in an attempt to accomplish this. The following therapeutic agents have been used: Nonspecific therapy, stimulating doses of roentgen rays,[446] sepsis and necrosis,[421] liver extract,[447] adenine sulphate,[448] pentnucleotide,[449] transfusions of blood [450] and leukocytic cream.[451]

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443. (*a*) Kastlin, G. J.: Agranulocytic Angina, Am. J. M. Sc. **173**:799, 1927. (*b*) Schultz, W., and Jacobowitz, L.: Agranulocytosis, Med. Klin. **21**: 1642, 1925. Millman, M., and Furcolo, C. L.: Relapsing Agranulocytosis with Case Report, New England J. Med. **208**:440, 1933.

444. Aubertin, C., and Levy, R.: L'agranulocytose et les syndromes agranulocytaires, Arch. d. mal. du coeur **21**:369, 1928. Footnote 421.

445. Lichtenstein, A.: Agranulozytose (Typus Schultz): (Granulocytopenia maligna), Acta med. Scandinav. (supp.) **49**:1, 1932. Footnote 443*a*.

446. (*a*) Friedemann, U., and Elkeles, A.: Die Roentgenbehandlung der Agranulozytose, Deutsche med. Wchnschr. **56**:947, 1930. (*b*) Taussig, A. E., and Schnoebelen, P. C.: Roentgen Treatment of Agranulocytosis, J. A. M. A. **97**:1757 (Dec. 12) 1931.

447. Foran, F. L.; Sheaff, H. M., and Trimmer, R. W.: Agranulocytic Angina: Treatment by Use of Parenteral and Oral Liver Extract; Preliminary Report, J. A. M. A. **100**:1917 (June 17) 1933. Coggeshall, L. T.: Neutropenia, "Agranulocytic Angina"; Report of Cases and Treatment, M. Clin. North America **17**:1645, 1934. von Bonsdorff, B.: Lebertherapie bei Granulocytopenia, Klin. Wchnschr. **13**:1079, 1934.

448. Resnikoff, P.: Adenine Sulphate Treatment of Agranulocytosis, J. Clin. Investigation **12**:45, 1933.

449. Jackson, H., Jr.; Parker, F., Jr., and Taylor, F. H. L.: Studies of Diseases of Lymphoid and Myeloid Tissues: Nucleotide Therapy of Agranulocytic Angina, Malignant Neutropenia and Allied Conditions; Analysis of Sixty-Nine Cases, Am. J. M. Sc. **184**:297, 1932.

450. Hueber, W.: Beitrag zur Frage der Agranulozytose, Frankfurt. Ztschr. f. Path. **40**:312, 1930. Footnote 428.

451. Strumia, M. M.: The Effect of Leukocytic Cream Injections in the Treatment of the Neutropenias, Am. J. M. Sc. **187**:527, 1934.

The evaluation of therapy in this disease is difficult, and anything which is said in regard to this at present must be tentative: This is because spontaneous recovery does occur in the disease, the patient who is treated may have secondary granulocytopenia instead of true granulocytosis, and drugs which have a deleterious effect, such as amidopyrine, may be administered simultaneously with the therapeutic agent. In brief, it may be said that roentgen treatment should be used with great caution because there may be an initial depression of the bone marrow before a stimulating effect occurs.[452] There is no convincing evidence that liver extract, nonspecific therapy, adenine sulphate or leukocytic cream is of therapeutic value. Multiple small transfusions of blood may be beneficial. There is no conclusive proof that they depress the bone marrow. There are more data in support of the effectiveness of pentnucleotide therapy than of any other form of treatment. In a group of 103 patients treated with this drug Jackson [424] reported a mortality of 33 per cent, as compared with a mortality of 76 per cent in a group of untreated patients reports of whose cases were compiled from the literature by Taussig and Schnoebelen,[446b] of 77 per cent as given by Brogsitter [426] and of 77 per cent as reported by Uffenorde.[453] Jackson and Parker [424] concluded that "at the present writing it would seem that pentnucleotide, provided there are no untoward reactions, offers the best chance of recovery in a patient with true agranulocytosis."

HEMATOLOGIC TECHNIC

A detailed account of progress in technic is out of place in a review devoted to the broader concepts of hematology. Brief mention will be made of a few methods and procedures of special interest without an attempt to furnish a complete bibliography.

In the study of the blood in cases of anemia increasing emphasis has been placed on correlation of the erythrocyte count, the hemoglobin level and the size of the erythrocytes. Although the value of such quantitative relationships was emphasized by Gram and Norgaard and Haden in 1923, they received little attention before the stimulation of interest in hematologic diagnosis occasioned by the advances of the past decade. Classifications of anemia based on the number, size and hemoglobin content of the red blood cells have been devised by Haden,[454]

452. Doan, Charles A.: The Neutropenic State: Its Significance and Therapeutic Rationale, J. A. M. A. **99**:194 (July 16) 1932.

453. Uffenorde, H.: Ausgedehnte Nekrotisierungen des Verdauungschlauches bei Agranulocytose nebst Bemerkungen über die ursächlichen Bedingungen dieser Erkrankung, Virchows Arch. f. path. Anat. **287**:555, 1932.

454. Haden, R. L.: Clinical Significance of Volume and Hemoglobin Content of the Red Blood Cell, Arch. Int. Med. **49**:1032 (June) 1932.

Osgood and Haskins [455] and Wintrobe.[456] Heller and Paul [457] have shown that the use, as an anticoagulant, or a mixture of ammonium oxalate, 6 parts, and potassium oxalate, 4 parts, does not alter the volume of the red cells. Two milligrams of the combined salts per cubic centimeter of blood are employed. This is an important contribution to the measurement of erythrocyte volume by the use in conjunction of the hematocrit value and the red cell count. Keller,[458] employing Bock's [459] modification of Pijper's diffraction method, determined the mean diameter of the erythrocytes of a large series of normal persons and found the range of the group to be from 7.30 to 7.76 microns, the average being 7.6 microns. He studied the size of the red cells of persons with pernicious anemia and correlated it with the blood count and the response to treatment. Of 45 patients with tuberculosis he found slight macrocytosis in 20 by the diffraction method.

Increasing interest in the iron deficiency anemias has inspired a number of recent clinical studies of iron in the blood.[460] It has not been convincingly demonstrated that the determination of the iron content of the circulating blood supplements information gained from accurate estimations of the hemoglobin content. Its chief value, as Haden [461] stated, is as a substitute for the test of oxygen capacity in the standardization of hemoglobinometers.[462]

The Wright and Giemsa staining methods have retained their popularity in the study of the morphology of the white blood cells. The supravital technic aids in the differentiation of cells in some types of

455. Osgood, E. E., and Haskins, H. D.: Causes, Classification and Differential Diagnosis of Anemias Based on Detailed Examination of Over Two Hundred Patients and Study of the Literature, Ann. Int. Med. **5**:1367, 1932.

456. Wintrobe, M. M.: Anemia: Classification and Treatment on Basis of Differences in Average Volume and Hemoglobin Content of Red Corpuscles, Arch. Int. Med. **54**:256 (Aug.) 1934.

457. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anti-Coagulants, J. Lab. & Clin. Med. **19**:777, 1934.

458. Keller, H. R.: Die klinische und praktische Bedeutung der Erythrocytendurchmesserbestimmung mit Hilfe der Diffraktionsmethode (Halometrie), unter besonderer Berücksichtigung der Perniciosa-Diagnose, Ztschr. f. klin. Med. **127**:132, 1934.

459. Bock, H. E.: Neue Möglichkeiten praktischer Anämiediagnostik (Ergebnisse der Erythrozytometrie), München. med. Wchnschr. **81**:1646, 1934.

460. Reich, C., and Tiedemann, V. G.: Study of "Iron Volume Index" of Blood and Its Significance in Treatment of Anemia, Am. J. M. Sc. **184**:637, 1932. Dowden, C. W., and McNeill, C.: Clinical Study of Blood Iron and Hemoglobin, J. Lab. & Clin. Med. **19**:362, 1934.

461. Haden, R. L.: Determination of Hemoglobin by Iron Content Method, J. Lab. & Clin. Med. **19**:406, 1934.

462. Broun, G. O., and Briggs, A. P.: Hemoglobin and Blood Cell Relations as Determined by Iron and Oxygen Capacity Methods, J. Lab. & Clin. Med. **19**:886, 1934.

leukemia, and it is especially applicable to the study of the monocyte response.[463] The Schilling index or one of its modifications is of recognized value in the study of the response to infection.[464] However, as Fitz-Hugh warned,[465] the information gained from its use is never more than suggestive and should be considered in relation to all other available data. Estimation of the erythrocyte sedimentation rate has become an increasingly popular procedure. Under controlled conditions it has definite value as an index of activity in pulmonary tuberculosis [466] and probably in rheumatic carditis.[467] The sedimentation test has been advocated as a routine procedure in preventive medicine in schools and institutions.[468]

In spite of its importance in a variety of hemorrhagic conditions the study of the blood platelets has been handicapped by a lack of technical procedures of easy application and proved worth. Methods of enumeration of the platelets have been excellently reviewed by Olef,[469] who believes that greatest accuracy is obtained by the use of true indirect methods involving the determination of the ratio of platelets to erythrocytes. He describes a technic of enumeration of the platelets based on this principle. Blacher [470] has classified blood platelets according to size and staining characteristics. He has made differential platelet counts

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463. Tompkins, E. H.: Clinical Application of Supra-Vital Staining, J. Lab. & Clin. Med. **17**:921, 1932.

464. Harkins, H. N.: Present Status of Blood Examination in Diagnosis of Surgical Infections with Study of Twenty-Seven Indices of Infection Reported in Literature, Surg., Gynec. & Obst. **59**:48, 1934. Case, J. W., Jr.: Schilling Differential Count and Red Cell Sedimentation Rate as Measurement of Activity in Pulmonary Tuberculosis, New England J. Med. **211**:252, 1934. Arvanitopulo, F. T.: Study of Morphology of White Corpuscles of Blood in Prognosis of Operations, Ann. Surg. **100**:11, 1934. Rogatz, J. L.: Schilling Blood Count as Aid in Diagnosis of Acute Appendicitis in Children, J. Pediat. **4**:757, 1934.

465. Fitz-Hugh, T., Jr.: Age of Leucocyte in Relation to Infection, J. Lab. & Clin. Med. **17**:975, 1932.

466. Ringer, P. H., and Roach, M.: Blood Sedimentation Test: Its Use as a Routine, Especially in Pulmonary Tuberculosis, Ann. Int. Med. **8**:258, 1934. Thiele, G.: Ueber den Wert der Bestimmung der Blutkörperchensenkungsgeschwindigkeit für die Diagnosen- und Prognosenstellung bei der Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **85**:302, 1934.

467. Perry, C. B.: Sedimentation Rate in Rheumatic Carditis, Arch. Dis. Childhood **9**:285, 1934.

468. Gallagher, J. R.: Value of the Blood Sedimentation Test in Routine Medical Examination of Adolescents and in Certain of Their Diseases, Am. J. M. Sc. **188**:450, 1934.

469. Olef, I.: Enumeration of Blood Platelets, J. Lab. & Clin. Med. **20**:416, 1935.

470. Blacher, L.: Recherches expérimentales sur les méthodes d'exploration et sur la morphologie des thrombocytes ainsi que sur leur importance clinique en tant que système autonome, Sang **9**:147, 1935.

on the blood of normal persons and in cases of anemias of different types, pulmonary tuberculosis, hyperthyroidism, Addison's disease, essential thrombocytopenic purpura and lymphatic leukemia. In these conditions he has found characteristic morphologic changes in the platelets as well as alterations in their total number.

A simplified procedure for obtaining sternal marrow in living persons consists of the introduction of a short needle with a thick bore at the sternomanubrial junction. A mixture of blood and bone marrow is readily obtained by aspiration and is suitable for the preparation of films stained by Wright's or, preferably, Giemsa's method. Young and Osgood [471] described the technic of this method, reported their observations from its use in health and in disease conditions and provided a complete bibliography. Reich [472] suggested that the fluid obtained by aspiration be centrifugated and films made from the buffy coat.

471. Young, R. H., and Osgood, E. E.: Sternal Marrow Aspirated During Life: Cytology in Health and in Disease, Arch. Int. Med. **55**:186 (Feb.) 1935.

472. Reich, C.: A Modified Technique for Sternal Puncture and Its Value in Hematologic Diagnosis, J. Lab. & Clin. Med. **20**:286, 1934.

Book Reviews

A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease. By Arthur R. Cushny. Tenth edition, thoroughly revised by C. W. Edmunds and J. A. Gunn. Price, $6.50. Pp. 786, with 75 illustrations. Philadelphia: Lea & Febiger, 1934.

The title and introduction to this book seem to indicate a duality of subjects: the one concerns pharmacology as a branch of biologic science, the other, as a method for the treatment of disease. Pharmacology is defined as the study of changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods; it is further stipulated that the drug must be introduced from without. The position of pharmacology in biologic science is described as follows: "Thus as physiology is the study of the life of the normal organism, pharmacology is the study of the organism rendered abnormal by drugs, while in pathology the phenomena of life under disease are examined." It is also stated that all three subjects may be pursued without reference to the practical needs of medicine. These delineations, in their present form, are not quite satisfactory. Pharmacology surrenders too much territory, and whether a potent agent is introduced into the organism from without or is produced within the organism seems rather immaterial. The antiseptic action of hydroxybutyric acid in infections of the urinary tract may be cited as a case in point. Later, happily, it is stated that the action of drugs must be studied in the diseased as well as in the healthy organism.

The reviewer grants that pharmacology need not concern itself solely with the practical needs of medicine, but considers that a greater intimacy is needed between pharmacology and medicine. Such intimacy is to the advantage of both and so to the advantage of the sick. And whatever else the goal may be, one cannot forget that the prevention, care and alleviation of sickness are the paramount issues of medicine, and that these issues largely determine the place of pharmacology in the medical school. This has not always been seen too clearly, with the unfortunate result that pharmacology as an independent branch of instruction is endangered, greatly to the detriment of both medicine and of pharmacology.

Thus the reviewer cannot emphasize too strongly, with the authors, that the great importance of pharmacology is not so much in its purely biologic aspects as in its significance in the treatment of disease, and that when the mode of action of a drug is understood much greater accuracy is attained in using it in treatment. "The object of pharmacology is to provide a scientific foundation for therapeutics and to increase the resources of the art of healing." If the authors mean by "art of healing" medicine, one can agree, but it might be well to emphasize that what medicine needs badly is less art and more healing, and that one looks to pharmacology for assistance in this.

Cushny's book has long been recognized as a standard text, so it is hardly necessary to state that it fully merits this revision by Edmunds and Gunn. They have done well. A few minor suggestions may be made. For instance, in speaking of methenamine it might be stated that the urine must be acidified to a given p_H and that this can be accomplished most readily by such salts as ammonium or calcium chloride. When giving crystalline hexylresorcinol, care has to be taken not to burn the mouth. The chapter on alcohol is singularly free from bias. It is stated, however, that the observations of Kraepelin with regard to the measurements of intellectual work lose much of their importance from the fact that the subjects knew when alcohol had been given them. The reviewer happened to be one of these subjects, and neither he nor his fellow subjects were influenced by suggestion. This was excluded by the arrangement of the experiments. Mild

mercurous chloride might still deserve a place among the purgatives, even if it is discussed under "Mercury." These are minor matters which in no way detract from the value of the book.

At the end is a classification of drugs based on their therapeutic uses, a welcome arrangement which facilitates the orientation of the reader.

The book can be recommended highly to both the student and the physician.

On the Ammonium Content of the Urine in Normal and Certain Pathologic Conditions, Especially in Patients with Convulsions. By Joergen Madsen. Pp. 215. Copenhagen: Levin & Munksgaard, 1933.

It appears from the literature that an abnormal acid-base equilibrium and an abnormal ammonia metabolism are frequently observed in cases of epilepsy. Controversial points are still under discussion. Madsen has limited his investigations to the urinary excretion of ammonia under varying conditions. He studied the p_H of the urine of normal persons and that of patients with convulsions and made the following observations: In patients who have convulsions, the average value for the p_H of the urine is higher and the variations from day to day are more marked. In normal persons, the daily range of the p_H of the urine is from below 6 in the morning to 7 later in the day. In patients with convulsions, the rise of the p_H in the latter part of the day is more marked. It almost always reaches alkaline values, a rare occurrence in normal persons. Alkali taken by mouth is more readily excreted in the urine of patients with convulsions than in that of normal persons.

Investigation of the excretion of ammonia in the urine revealed that the ammonium factor (the ammonium nitrogen-total nitrogen quotient) is, on the average, definitely increased in patients with convulsions and shows more marked variations from day to day than in normal persons. The excretion of ammonia was dependent on the p_H of the urine. Under normal conditions a rather constant relationship exists between the p_H and the ammonium nitrogen-total nitrogen quotient, and a somewhat less marked relationship between the p_H and the ammonium concentration of the urine. The ammonium nitrogen-total nitrogen quotient, as well as the total amount of ammonia excreted under conditions of constant urinary p_H, is higher in patients with convulsions than in normal persons.

Madsen discusses the so-called hyperbola regulation of Hasselbach, who found a relationship between the p_H of the urine and the ammonium nitrogen-total nitrogen quotient. The relationship is expressed by a hyperbolic curve. Madsen is in agreement with other authors in finding this hyperbolic regulation to be only approximately correct; however, the modified form of the hyperbola, the so-called regulation figure, gives the best expression at the present time for the relationship of the excretion of ammonia to the urinary p_H. In patients with convulsions, Madsen found increased values for the regulation figure.

The hyperammoniuria of persons with convulsions was not regularly accompanied by generalized acidosis. However, Madsen considers it possible that a disturbance of the acid-base equilibrium may be associated, since his investigations seem to indicate that the alkali in the tissues of the epileptic patient may be bound in some unusual manner so that at times retention of alkali occurs and at other times increased excretion. It is therefore assumed that the acid-regulating rôle of alkali is impaired in the organism of the epileptic person, resulting in the increased production of ammonia.

Madsen postulates a close relationship between hyperammoniuria and the precipitation of convulsions. Overventilation is more frequently followed by convulsions in patients with hyperammoniuria. Hyperammoniuria, it is assumed, is the result of an abnormality of metabolism which may be constitutional. It is understood that this is only one of the many factors of importance in the pathogenesis of convulsions.

Allergy and Applied Immunology: A Handbook for Physician and Patient, on Asthma, Hay Fever, Urticaria, Eczema, Migraine and Kindred Manifestations of Allergy. By Warren T. Vaughan. Second edition. Price, $5. Pp. 420, with 40 illustrations. St. Louis: C. V. Mosby Company, 1934.

The appearance of a second edition of a book within three years of first publication is good evidence that it has been received with favor. This is an excellent handbook for physician and patient on allergic conditions. The subject is presented with a thoroughness and simplicity that make it readily understandable to the average layman. An appendix of instructions, directions and forms has been added which should prove helpful in working out the causation of any particular case of allergy.

This presentation is recommended as a practical guide in the care of allergic persons. One can hardly praise it too highly.

Collens System of Diet Writing Including Diet Calculator. By William S. Collens. Price, $5. New York: Form Publishing Company, 1933.

Assembled in a loose-leaf folder are calculating cards for rapidly figuring all sorts of diets; lists of foods according to their content of vitamins, minerals and other constituents; brief lists of diets for various diseases, and, finally, a pad of blanks for prescribing diets. The reviewer is fascinated by the calculating cards. By spinning a wheel or sliding cards in and out past slits one can instantly formulate an almost limitless variety of diets.

News and Comment

NATIONAL ASSOCIATION FOR PREVENTION OF TUBERCULOSIS IN ENGLAND

The National Association for the Prevention of Tuberculosis of England will hold its twenty-first annual conference at Southport, June 27 to 29. The subject for discussion will be "The Responsibility of the Nation Toward the Child in Respect of Tuberculosis."

CORRECTION

In the article by Drs. Necheles and Coyne, entitled, "Secretion of Mucus and Acid by the Stomach in Healthy Persons and in Persons with Peptic Ulcer," in the March issue (ARCH. INT. MED. **55**:395, 1935), "(P = 0.54)" in the fifth line of the fourth paragraph on page 399 should read "(P = 0.054)."

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